

**WARNING: CONGESTIVE HEART FAILURE AND Lactic Acidosis**

See full prescribing information for complete boxed warning.

**CONGESTIVE HEART FAILURE**

- Thiazolidinediones, including pioglitazone, which is a component of pioglitazone and metformin hydrochloride tablets, cause or exacerbate congestive heart failure in some patients. (3, 4)

- After initiation of pioglitazone and metformin hydrochloride tablets, and after dose increases, monitor for symptoms of congestive heart failure, especially in patients with risk factors such as prior cardiovascular disease, NYHA Class II heart failure, or hemoglobin <10 g/dL. If congestive heart failure occurs or worsens, stop pioglitazone and metformin hydrochloride tablets and manage according to accepted standards of care and rechallenge with a reduced dose of pioglitazone and metformin hydrochloride tablets on a case-by-case basis. (3, 4)

- Pioglitazone and metformin hydrochloride tablets are not recommended in patients with New York Heart Association (NYHA) Class III or IV heart failure. (3, 4)

**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)

**CONTRAINDICATIONS**

**Use in Patients with Established New York Heart Association (NYHA) Class III or IV Heart Failure**

Pioglitazone and metformin hydrochloride tablets are not recommended in patients with established New York Heart Association Class III or IV heart failure. (4)

**Use in Patients with Severe Renal Impairment**

Pioglitazone and metformin hydrochloride tablets are not recommended in patients with severe renal impairment (eGFR below 30 mL/min/1.73 m²). (4)

**Use in Patients with Impaired Hepatic Function**

Pioglitazone and metformin hydrochloride tablets are not recommended in patients with known hepatic disease or who have a history of significant hepatic disease. (4)

**Use in Patients with Hypersensitivity to Pioglitazone or Metformin**

Pioglitazone and metformin hydrochloride tablets are not recommended in patients with hypersensitivity to pioglitazone, metformin, or any other component of pioglitazone and metformin tablets. (4)

**Use in Patients with Known Informed Consent for Use of Pioglitazone and metformin tablets**

Because of the potential for hepatic failure that may be fatal, obtain liver tests before initiating pioglitazone and metformin hydrochloride tablets. If abnormal, use caution when initiating pioglitazone and metformin hydrochloride tablets. (5.5)

**Monitor Patients for Adverse Events Related to Fluid Retention**

Pioglitazone and metformin hydrochloride tablets may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures. (2.1, 5.5)

**DOSAGE FORMS AND STRENGTHS**

Tablets: 1 mg pioglitazone/85 mg metformin hydrochloride and 15 mg pioglitazone/1000 mg metformin hydrochloride tablets. (2.1)

**RECENT MAJOR CHANGES**

**DRUG INTERACTIONS**

- Strong CYP2C8 inhibitors (e.g., gemfibrozil) increase pioglitazone concentrations. Limit pioglitazone and metformin tablets to the maximum recommended dose. (7.5)

- Topiramate may decrease pioglitazone concentrations. (7.8)

- Strong induction of cytochrome P450 enzymes (e.g., rifampin) may decrease pioglitazone concentrations. (7.2)

- Certain antifungal inhibitors may increase risk of hypoglycemia. (7.3)

- Drugs that reduce melanoma incidence (such as celebrex, celecoxib, diclofenac, and etoricoxib) may increase the incidence of melanoma. (7.4)

- Alcohol can potentiate the effect of metformin on lactate metabolism. (5.2)

- Use of insulin or insulin secretagogues may increase the risk of hypoglycemia. (5.10)

- Use of insulin or insulin secretagogues may increase the risk of hypoglycemia. (5.10)

**SIDE EFFECTS**

**Most Common Adverse Reactions**

- The most common adverse reactions (>5%) are urinary tract infection, edema, diarrhea, headache, and weight gain. (3)

**Special Populations**

- Children: The safety and effectiveness of pioglitazone and metformin tablets in children have not been established. (5.1)

**Disclaimer**

This summary does 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.
5.8 Macular Edema
5.9 Vitamin B12 Levels
5.10 Macular Degeneration

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience

7 DRUG INTERACTIONS
7.1 Strong CYP3A4 Inhibitors
7.2 CYP3A4 Inducers
7.3 Carbonic Anhydrase Inhibitors
7.4 Drugs that Reduce Metformin Clearance
7.5 Alcohol
7.6 Advil, ibuprofen, or other nonsteroidal anti-inflammatory drugs
7.7 Drugs Affecting Glycemic Control

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES
14.1 Patients Previously Treated with Metformin
14.2 Patients Previously Treated with Thiazolidinediones

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

FULL PRESCRIBING INFORMATION

WARNING: CONGESTIVE HEART FAILURE AND LACTIC ACIDOSIS

Congestive Heart Failure

- Thiazolidinediones, including pioglitazone and metformin hydrochloride tablets, cause or exacerbate congestive heart failure in some patients [see Warnings and Precautions (5.1)].
- After initiation of pioglitazone and metformin hydrochloride tablets, and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., dyspnea, edema, and weight gain). If heart failure develops, it should be managed according to current standards of care and/or discontinuation or dose reduction of pioglitazone and metformin hydrochloride tablets must be considered [see Warnings and Precautions (5.2)].
- Pioglitazone and metformin hydrochloride tablets are not recommended in patients with symptoms of congestive heart failure [see Warnings and Precautions (5.1)].
- Initiation of pioglitazone and metformin hydrochloride tablets in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated [see Contraindications (4) and Warnings and Precautions (5.1)].

Lactic Acidosis

- Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hyperkalemia, hypoxia, and overt renal failure. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgia, respiratory distress, tachypnea, and abdominal pain.
- Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (greater than 5 mmol/L), anion gap acidosis (without evidence of ketoacidosis or ketoamilia), an increased lactate/pyruvate ratio, and metformin plasma levels generally greater than 5 mcg/mL [see Warnings and Precautions (5.2)].
- Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as acetazolamide), age 65 years old or greater, having a radiological study with contrast, surgery and/or other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.
- Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high-risk groups are provided in the Full Prescribing Information [see Dosage and Administration (12.1), Contraindications (4), Warnings and Precautions (5.2), Drug Interactions (7), and Use in Specific Populations (8.6, 8.7)].
- If metformin-associated lactic acidosis is suspected, immediately discontinue pioglitazone and metformin hydrochloride tablets and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended [see Warnings and Precautions (5.2)].

1 INDICATIONS 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 exerted an 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 (5.3)].

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/1000 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 II congestive heart failure: 15 mg/1000 mg or 15 mg/500 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/1000 mg once daily and/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/1000 mg once daily and/or twice daily (depending on the dose of pioglitazone already being taken) 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 2000 mg of metformin.

If treatment with pioglitazone and metformin is considered appropriate the recommended starting dose is:
- 15 mg/500 mg twice daily or 15 mg/1000 mg once daily and gradually titrated, as needed, after assessing adequacy of therapeutic response and tolerability,
- For patients with NYHA Class I or II congestive heart failure: 15 mg/1000 mg or 15 mg/500 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/1000 mg once daily and/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/1000 mg once daily and/or twice daily (depending on the dose of pioglitazone already being taken) 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 2000 mg of metformin.

Pioglitazone doses above 30 mg may be better tolerated given three times a day.

After initiation of pioglitazone and metformin hydrochloride tablets or with dose increase, monitor patients carefully for adverse reactions related to fluid retention such as weight gain, edema, and symptoms of congestive heart failure [see Warnings and Precautions (5.1)].

Liver tests (serum alanine and aspartate aminotransferase, 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 is 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
Hypoxic States

be temporarily discontinued while patients have restricted food and fluid intake.

depletion, hypotension and renal impairment. Pioglitazone and metformin hydrochloride tablets should

Withholding of food and fluids during surgical or other procedures may increase the risk for volume

alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-

an eGFR between 30 and 60 mL/min/1.73 m

decrease in renal function and the occurrence of lactic acidosis. Stop pioglitazone and metformin

Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute

Radiological Studies with Contrast

Age 65 or Greater

cationic drugs)

The concomitant use of pioglitazone and metformin hydrochloride with specific drugs may increase the

Drug Interactions

Lactic Acidosis

Lactic Acidosis

There have been post-marketing cases of metformin-associated lactic acidosis, including fatal cases.

These cases had a sudden onset and were accompanied by nonspecific symptoms such as malaise, myalgia, abdominal pain, respiratory distress, or increased summation; however, hyperventilation, hypocalcemia and severe hypophosphatemia have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (greater than 5 mmol/L), an increased anion gap (without evidence of ketonuria or ketonemia), and an increased lactate:pyruvate ratio/metformin plasma levels generally greater than 5 mmol/L. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of pioglitazone and metformin hydrochloride tablets. In pioglitazone and metformin hydrochloride tablets-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Patients and their families should be informed of the symptoms and the need to seek medical assistance promptly if they occur.

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

Renal Impairment

The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include (see Dosage and Administration (2.2), Clinical Pharmacology (12.3)).

Before initiating pioglitazone and metformin hydrochloride tablets, obtain an eGFR.

Pioglitazone and metformin hydrochloride tablets are contraindicated in patients with an eGFR less than 30 mL/min/1.73 m. Initiation of pioglitazone and metformin hydrochloride tablets is not recommended in patients with an eGFR between 30 to 45 mL/min/1.73 m (see Contraindications (4)).

Obtain an eGFR at least annually in all patients taking pioglitazone and metformin hydrochloride tablets. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

In patients taking pioglitazone and metformin hydrochloride tablets whose eGFR later falls below 45 mL/min/1.73 m, assess the benefit and risk of continuing therapy.

Drug Interactions

The concomitant use of pioglitazone and metformin hydrochloride with specific drugs may increase the risk of metformin-associated lactic acidosis; those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation (e.g. cationic drugs) (see Drug Interactions (7.7)).

In patients with impaired renal function, pioglitazone and metformin hydrochloride tablets should be temporarily discontinued while patients have restricted food and fluid intake.
Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiomyopathy (‘black’, acute myocardial infarction, reperfusion, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause peripheral anemia. When such events occur, discontinue pioglitazone and metformin hydrochloride tablets.

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

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

5.3 Edema
In controlled clinical trials with pioglitazone, edema was reported more frequently in patients treated with pioglitazone than in placebo-treated patients and in 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-secreting agents such as sulfonylureas) may be at risk for hypoglycemia. A reduction in the dose of the concomitant antidiabetic medcication may be necessary to reduce the risk of hypoglycemia [see Drug Interactions (7.7)]. Hypoglycemia can also occur when caloric intake is deficient or when strenuous exercise is not compensated by caloric supplement.

Elderly, debilitated, or malnourished patients, and those with atrial or sinus tachycardia 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 hepatitis in the pioglitazone controlled clinical trial database to date [see Adverse Reactions (6.6)].

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 are 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 should be initiated to establish the probable cause. Pioglitazone and metformin hydrochloride should not be renewed 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 reconstituted on pioglitazone and metformin hydrochloride. For patients with lower elevation of serum ALT or bilirubin with an alternate probable cause, treatment with pioglitazone and metformin hydrochloride can be used with caution.

5.6 Urinary Bladder Tumors
Tumors were observed in the urinary bladder of male rats in the two-year carcinogeticity study [see Nonclastotic Toxicology (13.2)]. In addition, during the three-year PROactive clinical trial, 16 patients out of 2035 (0.54%) randomized to pioglitazone and 5 out of 2463 (0.19%) randomized to placebo were diagnosed with bladder cancer. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 6 (0.27%) cases on pioglitazone and two (0.08%) cases on placebo. After completion of the trial, a large subset of patients was observed for up to 10 additional years, with little additional exposure to pioglitazone. During the 13 years of both PROactive and observational follow-up, the occurrence of bladder cancer did not differ between patients randomized to pioglitazone or placebo (HR = 1.00 [95% CI: 0.59 to 1.72]).

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

A large prospective 10-year observational cohort study conducted in the United States found no statistically significant increase in the risk of bladder cancer in diabetic patients ever exposed to pioglitazone, compared to those never exposed to pioglitazone (HR = 1.06 [95% CI: 0.89 to 1.26]).

A retrospective cohort study conducted with data from the United Kingdom found a statistically significant association between ever exposure to pioglitazone and bladder cancer (HR: 1.63; [95% Cl: 1.22 to 2.13]).

Association between cumulative dose or duration of exposure to pioglitazone and bladder cancer were not detected in studies including the Systolic Hypertension in Elders Study (Syst-Eur) observational study in the U.S., but were in others. Inconsistent findings and limitations inherent to other and other studies preclude conclusive interpretation of the observational data.

Pioglitazone may be associated with an increase in the risk of urinary bladder tumors. There are insufficient data to determine whether pioglitazone is a tumor promoter for urinary bladder tumors. Consequently, pioglitazone and metformin hydrochloride tablets should not be used in patients with active bladder cancer and the benefits of glycemic control versus unknown risks for cancer recurrence with pioglitazone and metformin hydrochloride tablets should be considered in patients with a prior history of bladder cancer.

5.7 Fractures
In PROactive (the Prospective Pioglitazone Clinical Trial in Macrovascular Events), 5238 patients with type 2 diabetes and a history of macrovascular disease were randomized to pioglitazone (N=2055), force-titrated to 45 mg daily or placebo (N=2583) in addition to standard of care. During a mean follow-up of 3.5 years, the incidence of bone fracture in women was 3.4% (44/1298) for pioglitazone versus 2.5% (25/985) 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 vertebral fractures including lesser thoracic and dorsal upper lumbar. No increase in the incidence of fracture was observed in men compared with pioglitazone (0.7%) 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 ophthalmic 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 (6.6)].

5.9 Vitamin B12 Levels
In controlled clinical trials of metformin of 29 weeks’ duration, a decrease in subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestion, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-cobalamin complex, is, however, very rarely associated with amnesia and appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on pioglitazone and metformin hydrochloride tablets and any apparent abnormalities should be appropriately investigated and managed.

Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be...
6. ADVERSE REACTIONS

The following serious adverse reaction 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 (5.3)]
- Edema [see Warnings and Precautions (5.5)]
- Fractures [see Warnings and Precautions (5.7)]

6.1 Clinical Trials Experience

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

Pioglitazone

Over 8500 patients with type 2 diabetes have been treated with pioglitazone in uncontrolled, double-blind, controlled clinical trials, including 3005 patients with type 2 diabetes and macrovascular disease treated with pioglitazone from the PROActive clinical trial. In these trials, over 8000 patients have been treated with pioglitazone for six months or longer, over 4500 patients have been treated with pioglitazone for one year or longer, and over 3000 patients have been treated with pioglitazone for at least two years.

In 16- to 26-week placebo-controlled monotherapy and 16- to 24-week add-on combination therapy trials, the incidence of withdrawals due to adverse events was 4.5% for patients treated with pioglitazone and 5.8% for comparator-treated patients. The most common adverse events leading to withdrawal were related to inadequate glycemic control, although the incidence of these events was lower (1.5%) with pioglitazone than with placebo (3.0%).

In the PROactive trial, the incidence of withdrawals due to adverse events was 9.0% for patients treated with pioglitazone and 7.7% for placebo-treated patients. Congestive heart failure was the most common serious adverse event leading to withdrawal occurring in 1.3% of patients treated with pioglitazone and 0.0% of patients treated with placebo.

6.2 Common Adverse Events: 24-Week Pioglitazone and Metformin Hydrochloride Tablets Clinical Trial

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 in patients treated with pioglitazone than in patients who received placebo. None of these adverse events were related to the pioglitazone dose.

6.3 Common Adverse Events: 16- to 26-Week Monotherapy Trials

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

<table>
<thead>
<tr>
<th>Incidence (%)</th>
<th>Placebo N=259</th>
<th>Pioglitazone N=263</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>8.5</td>
<td>13.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.9</td>
<td>9.5</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3.1</td>
<td>5.4</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>0.0</td>
<td>5.1</td>
</tr>
</tbody>
</table>

6.4 Common Adverse Events: 16- to 26-Week Add-on Combination Therapy Trials

Table 2. 16- to 24-Week Clinical Trials of Pioglitazone Add-on to Metformin

<table>
<thead>
<tr>
<th>Incidence (%)</th>
<th>Placebo N=160</th>
<th>Pioglitazone 75 mg N=30</th>
<th>Placebo N=168</th>
<th>Pioglitazone 30 mg N=411</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>2.5</td>
<td>1.9</td>
<td>5.4</td>
<td>2.9</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Weight Increased</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

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

6.5 Common Adverse Events: 24-Week Pioglitazone and Metformin Hydrochloride Tablets 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 tablets dosed twice daily in patients with inadequate glycemic control on diet and exercise (N=600).

Table 3. Adverse Events (≥5% for ACTOPLUS ME!) Reported by Patients with Inadequate Glycemic Control on Diet and Exercise in a 24-Week Double-Blind Clinical Trial of Pioglitazone and Metformin Hydrochloride Tablets Administered Twice Daily

<table>
<thead>
<tr>
<th>Incidence (%)</th>
<th>Pioglitazone and Metformin Hydrochloride Tablets 15/50 mg Twice Daily N=201</th>
<th>Pioglitazone 15 mg Twice Daily N=101</th>
<th>Metformin 50 mg Twice Daily N=200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>9.0</td>
<td>2.6</td>
<td>13.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.5</td>
<td>2.6</td>
<td>4.0</td>
</tr>
</tbody>
</table>

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

6.6 Common Adverse Events: PROActive Trial

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

Table 4. PROActive Trial Incidence and Types of Adverse Events Reported in ≥5% of Patients Treated with Pioglitazone and More Commonly than Placebo

<table>
<thead>
<tr>
<th>Incidence (%)</th>
<th>Placebo N=2003</th>
<th>Pioglitazone N=2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>88.8</td>
<td>27.3</td>
</tr>
<tr>
<td>Edema</td>
<td>15.3</td>
<td>26.7</td>
</tr>
<tr>
<td>Cardio Failure</td>
<td>8.1</td>
<td>8.1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5.7</td>
<td>4.4</td>
</tr>
<tr>
<td>Back Pain</td>
<td>5.1</td>
<td>5.5</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>5.0</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Note: The preferred term of edema peripheral, generalized edema, and fluid retention were combined to form the aggregate term of “edema.”
A summary of the incidence of adverse events related to congestive heart failure is provided in Table 5 for the 16- to 24-week add-on to metformin trials. None of the events were fatal.

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo-Controlled Trial (18 weeks)</th>
<th>Pioglitazone 30 mg or Metformin N=188</th>
<th>Pioglitazone 45 mg or Metformin N=191</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one congestive heart failure event</td>
<td>0 (0.0%)</td>
<td>1 (0.6%)</td>
<td>0 (0.2%)</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>0 (0.0%)</td>
<td>1 (0.6%)</td>
<td>0 (0.2%)</td>
</tr>
</tbody>
</table>

### Table 6. Treatment-Emergent Adverse Events of Congestive Heart Failure (CHF) in Patients Treated with Pioglitazone or Placebo Added on to a Sulfonylurea

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo-Controlled Trial (18 weeks)</th>
<th>Pioglitazone 15 mg or Sulfonylurea N=195</th>
<th>Pioglitazone 30 mg or Sulfonylurea N=201</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one congestive heart failure event</td>
<td>2 (1.5%)</td>
<td>2 (1.0%)</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>2 (1.5%)</td>
<td>2 (1.0%)</td>
<td>2 (1.0%)</td>
</tr>
</tbody>
</table>

### 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 Glimepiride

<table>
<thead>
<tr>
<th>Event</th>
<th>Pioglitazone N=2682</th>
<th>Glimepiride N=2630</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of Subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death due to cardiovascular causes</td>
<td>5 (1.9%)</td>
<td>6 (2.3%)</td>
</tr>
<tr>
<td>(adjudicated)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overnight hospitalization for worsening CHF (adjudicated)</td>
<td>26 (9.9%)</td>
<td>12 (4.7%)</td>
</tr>
<tr>
<td>Emergency room visit for CHF (adjudicated)</td>
<td>4 (1.5%)</td>
<td>31 (12.2%)</td>
</tr>
<tr>
<td>Patients experiencing CHF progression during study</td>
<td>35 (13.4%)</td>
<td>21 (8.2%)</td>
</tr>
</tbody>
</table>

### Cardiovascular Safety

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

The primary objective of this trial was to examine the effect of pioglitazone on mortality and macrovascular events with pioglitazone. The number of first occurrences and total individual events contributing to the primary composite endpoint is shown in Table 5.

### Table 8. Treatment-Emergent Adverse Events of Congestive Heart Failure (CHF) in PROactive Trial

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo N=2633</th>
<th>Pioglitazone N=2605</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one hospitalized congestive heart failure event</td>
<td>108 (4.1%)</td>
<td>149 (5.7%)</td>
</tr>
<tr>
<td>Final</td>
<td>22 (0.8%)</td>
<td>28 (1.0%)</td>
</tr>
<tr>
<td>Hospitalized, not fatal</td>
<td>85 (3.3%)</td>
<td>124 (4.7%)</td>
</tr>
</tbody>
</table>

### Cardiac Events in the PROactive Trial

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

The primary objective of this trial was to examine the effect of pioglitazone on mortality and macrovascular events with pioglitazone. The number of first occurrences and total individual events contributing to the primary composite endpoint is shown in Table 5.

### Table 9. PROactive Trial Number of First and Total Events for Each Component within the Cardiovascular Composite Endpoint

<table>
<thead>
<tr>
<th>Cardiovascular Events</th>
<th>Placebo N=2633</th>
<th>Pioglitazone N=2605</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>552 (21.7%)</td>
<td>502 (19.7%)</td>
</tr>
<tr>
<td>Total events</td>
<td>900</td>
<td>803</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>122 (4.6%)</td>
<td>158 (6.2%)</td>
</tr>
<tr>
<td>Total cardiovascular events</td>
<td>115 (4.4%)</td>
<td>151 (5.8%)</td>
</tr>
<tr>
<td>Total events</td>
<td>118 (4.5%)</td>
<td>151 (5.8%)</td>
</tr>
<tr>
<td>Acute myocardial infarction (MI)</td>
<td>118 (4.5%)</td>
<td>151 (5.8%)</td>
</tr>
<tr>
<td>Total events</td>
<td>118 (4.5%)</td>
<td>151 (5.8%)</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>63 (2.4%)</td>
<td>71 (2.7%)</td>
</tr>
<tr>
<td>Total events</td>
<td>63 (2.4%)</td>
<td>71 (2.7%)</td>
</tr>
<tr>
<td>Major leg amputation</td>
<td>15 (0.6%)</td>
<td>28 (1.0%)</td>
</tr>
<tr>
<td>Total events</td>
<td>15 (0.6%)</td>
<td>28 (1.0%)</td>
</tr>
<tr>
<td>Leg revascularization</td>
<td>57 (2.2%)</td>
<td>92 (3.5%)</td>
</tr>
<tr>
<td>Total events</td>
<td>57 (2.2%)</td>
<td>92 (3.5%)</td>
</tr>
</tbody>
</table>
Weight Gain

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

Table 10. Weight Changes (kg) from Baseline During Randomized, Double-Blind Clinical Trials

<table>
<thead>
<tr>
<th>Monotherapy (16 to 26 weeks)</th>
<th>Pioglitazone 15 mg</th>
<th>Pioglitazone 30 mg</th>
<th>Pioglitazone 45 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (25th, 75th percentile)</td>
<td>-1.4 (-2.7, 0.0)</td>
<td>0.0 (-0.5, 3.4)</td>
<td>1.0 (-0.9, 3.4)</td>
</tr>
<tr>
<td>N=256</td>
<td>36 (25th, 75th percentile)</td>
<td>39 (25th, 75th percentile)</td>
<td>38 (25th, 75th percentile)</td>
</tr>
<tr>
<td>Combination Therapy (16 to 26 weeks)</td>
<td>Sulfonylurea</td>
<td>Metformin</td>
<td>Insulin</td>
</tr>
<tr>
<td>Median (25th, 75th percentile)</td>
<td>2.0 (0.2, 3.3)</td>
<td>0.0 (0.3, 3.3)</td>
<td>3.3 (0.0, 6.0)</td>
</tr>
<tr>
<td>N=363</td>
<td>32 (25th, 75th percentile)</td>
<td>37 (25th, 75th percentile)</td>
<td>52 (25th, 75th percentile)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Pioglitazone 15 mg Twice Daily</th>
<th>Pioglitazone 30 mg Twice Daily</th>
<th>Pioglitazone 45 mg Twice Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (25th, 75th percentile)</td>
<td>-1.0 (-1.1, 0.0) N=108</td>
<td>1.35 (-0.7, 4.1) N=178</td>
<td>-1.00 (-2.6, 0.4) N=203</td>
</tr>
</tbody>
</table>

Edema

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

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

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

Table 12. Weight Changes (kg) from Baseline During Double-Blind Clinical Trials with Pioglitazone and Metformin Hydrochloride Tablets in Patients with Inadequate Glycemic Control on Diet and Exercise

<table>
<thead>
<tr>
<th>Pioglitazone and Metformin Hydrochloride Tablets</th>
<th>Pioglitazone 15 mg Twice Daily</th>
<th>Pioglitazone 30 mg Twice Daily</th>
<th>Pioglitazone 45 mg Twice Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (25th, 75th percentile)</td>
<td>-1.0 (-1.1, 0.0) N=108</td>
<td>1.35 (-0.7, 4.1) N=178</td>
<td>-1.00 (-2.6, 0.4) N=203</td>
</tr>
</tbody>
</table>

Hepatic Effects

There has been no evidence of pioglitazone-induced hepatotoxicity in the pioglitazone controlled clinical trial database to date. One randomized, double-blind, three-year trial comparing pioglitazone in glyburide as add-on to metformin and insulin therapy was specifically designed to evaluate the incidence of severe ALT elevations greater than three times the upper limit of the reference range, measured every eight weeks for the first 48 weeks of the trial then every 12 weeks thereafter. A total of 3,351 patients (25% of patients) treated with pioglitazone and 3,046 (21%) 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 severe 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 0.3% with placebo. In the 16-week add-on to insulin, 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%).

These patients increase four trials were hospitalized due to hypoglycemia. All these patients were receiving pioglitazone 30 mg (3.5%) 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 (4 vs 2) with pioglitazone 30 mg or 45 mg in combination with insulin (p<12).

Urinary Bladder Tumors

Tumors were observed in the urinary bladder of male rats in the two-year carcinogenicity study (see Sectional Toxicology (13.7.1)). During the three year PROActive clinical trial, 14 patients out of 2605 (0.55%) randomized to pioglitazone and 5 out of 203 (2.49%) randomized to placebo were diagnosed with bladder cancer. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 6 (0.2%) cases on pioglitazone and two (0.1%) cases on placebo. After completion of the trial, a large subset of patients was observed for up to 10 additional years, with little additional exposure to pioglitazone. During the 13 years of both PROActive and observational follow-up, the occurrence of bladder cancer did not differ between patients randomized to pioglitazone or placebo (HR =1.00; 95% CI: 0.39 to 1.72) (see Warnings and Precautions (15.4)).

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 141 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.

### 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 to a mean change in hemoglobin of 1% to 2% 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\(_6\) Concentrations

Metformin lowers serum vitamin B\(_6\) concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on pioglitazone and metformin or hydrochloride and any apparent abnormalities should be appropriately investigated and managed [see Warnings and Precautions (5.9)].

#### Creatine Phosphokinase

During protocol-specified measurement of serum creatine phosphokinase (CPK) in pioglitazone clinical trials, an isolated elevation in CPK to greater than 10 times the upper limit of the reference range was noted in 0.2% of patients treated with pioglitazone (values of 250 to 1140 IU/L) and in no placebo-treated patients. Six of these nine patients continued to receive pioglitazone; two patients were noted to have the CPK elevation on the last day of dosing, and one patient discontinued pioglitazone due to the elevation. These elevations resolved without any apparent clinical sequelae.

The relationship of these events to pioglitazone therapy is unknown.

### 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of pioglitazone. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

#### Pioglitazone

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

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 concurrent insulin administered.

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 Based Warning and Precautions (5.1)].

#### Methotrexate

Chloasma, hyperpigmentation, and increased hepatic lipid injury.

### 7 DRUG INTERACTIONS

#### 7.1 Strong CYP2C8 Inhibitors

An inhibitor of CYP2C8 (e.g., gemfibrozil) significantly increases the exposure (area under the serum concentration-time curve or AUC) and half-life (t\(_{1/2}\)) 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 concentration-time curve or AUC) and half-life (t\(_{1/2}\)) of pioglitazone due to the elevation. These elevations resolved without any apparent clinical sequelae. The relationship of these events to pioglitazone therapy is unknown.

#### 7.3 Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with pioglitazone and metformin hydrochloride may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients.

#### 7.4 Drugs that Reduce Metformin Clearance

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter 2 [OCT2] modulating and tissue variation [MATE] inhibitors such as candesartan, valsartan, delapril, and cilnidipine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis [see Clinical Pharmacology (12.3)].

#### 7.5 Alcohol

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

#### 7.6 Insulin Secretagogues or Insulin

If hyperglycemia occurs in a patient coadministered pioglitazone and metformin hydrochloride and an insulin secretagogue (e.g., sulfonylurea), the dose of the insulin secretagogue should be reduced. If hyperglycemia occurs in a patient coadministered pioglitazone and metformin hydrochloride and an insulin, the dose of insulin should be decreased by 30% to 50%. Further adjustments to the insulin dose should be individualized based on glycemic response.

#### 7.7 Drugs Affecting Glycemic Control

Certain drugs used to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, conjugated estrogens, oral contraceptives, phenytoin, sodium valproate, thiazolidinediones (rosiglitazone, pioglitazone), and isoniazid. When such drugs are administered to a patient receiving pioglitazone and metformin hydrochloride tablets, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving pioglitazone and metformin hydrochloride tablets, the patient should be observed closely for hypoglycemia.

#### 7.8 Topiramate

A decrease in the exposure of pioglitazone and its active metabolites were noted when topiramate was coadministered in pregnant rats and rabbits during organogenesis at exposures up to 5 and 35 times the 45 mg clinical dose, respectively, based on body surface area. No adverse developmental effects were noted in animal reproduction studies. When topiramate was administered to pregnant rats and rabbits during organogenesis at exposures up to 5 and 35 times the 45 mg clinical dose, respectively, based on body surface area. No adverse developmental effects were noted in animal reproduction studies.

#### 7.9 Other Drug Interactions

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter 2 [OCT2] modulating and tissue variation [MATE] inhibitors such as candesartan, valsartan, delapril, and cilnidipine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis [see Clinical Pharmacology (12.3)].

#### 7.10 Antacids

Antacids such as aluminum hydroxide and magnesium hydroxide frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with pioglitazone and metformin hydrochloride may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients.

#### 7.11 Oral Contraceptives

Oral contraceptives such as conjugated estrogens, oral contraceptives, and oral contraceptives such as ethinyl estradiol, may increase the risk for hypoglycemia. Concomitant use of these drugs with pioglitazone and metformin hydrochloride may increase the risk for hypoglycemia. Consider more frequent monitoring of these patients.

#### 7.12 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 concentration-time curve or AUC) and half-life (t\(_{1/2}\)) of pioglitazone due to the elevation. These elevations resolved without any apparent clinical sequelae. The relationship of these events to pioglitazone therapy is unknown.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

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

In animal reproduction studies, no adverse developmental effects were observed when pioglitazone was administered to pregnant rats and rabbits during organogenesis at exposures up to 5 and 35 times the 45 mg clinical dose, respectively, based on body surface area. No adverse developmental effects were observed.
observed when metformin was administered to pregnant Sprague Dawley rats and rabbits during the period of organogenesis at doses up to 25% to 50% of the 45 mg clinical dose, respectively, a 2000 mg clinical dose, based on body surface area [see Data].

The estimated background risk of major birth defects in 6 to 10% in women with pregestational diabetes with a HbA1c >7 and has been reported to be as high as 20 to 25% in women with a HbA1c >10. The estimated background risk of miscarriage in the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 5 to 15%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

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

Data

Human Data

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

Animal Data

Pioglitazone and Metformin hydrochloride

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

Pioglitazone

Pioglitazone administered to pregnant rats during organogenesis did not cause adverse developmental effects at a dose of 20 mg/kg (6-times the 45 mg clinical dose), did not alter maternal body weight, occurred in offspring at maternal doses of 10 mg/kg or 60 mg/kg (25.4% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, these studies were not designed to definitely establish the risk of use of metformin reducing, lactation because of sample size and limited adverse event data collected in infants.

8.2 Lactation

Risk Summary

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

Data

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

8.3 Females and Males of Reproductive Potential

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

8.4 Pediatric Use

Safety and effectiveness of pioglitazone and metformin hydrochloride in pediatric patient 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, 5.2, 5.3, 5.4, 5.7)].

8.5 Geriatric Use

Pioglitazone

A total of 92 patients (15.2%) treated with pioglitazone in the three pooled 16- to 26-week double-blind placebo-controlled, monotherapy trials were ≥65 years old and two patients (0.3%) were ≥75 years old. In the two pooled 16- to 24-week add-on to metformin trials, 155 patients (15.5%) treated with pioglitazone were ≥65 years old and 19 (1.8%) were ≥75 years old. In the two pooled 16- to 24-week add-on to insulin trials, 272 patients (26.4%) treated with pioglitazone were ≥65 years old and 22 (2.1%) were ≥75 years old.

In an active-controlled, 1018 patients (41.9%) treated with pioglitazone ≥65 years old and 42 (1.6%) were ≥75 years old.

In pharmacokinetic studies with pioglitazone, no significant differences were observed in pharmacokinetic parameters between elderly and younger patients [see Clinical Pharmacology (12.3)].

Although clinical experiences have not identified differences in effectiveness and safety between the elderly (<65 years) and younger patients, these conclusions are limited by small sample sizes for patients ≥75 years old.

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience with other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients [see Warnings and Precautions (5.2) and Drug Interactions (2.2)]

8.6 Renal Impairment

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Pioglitazone and metformin hydrochloride tablets are contraindicated in severe renal impairment, patients with eGFR below 30 ml/min/1.73 m² [see Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]

8.7 Hepatic Impairment

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

10 OVERDOSAGE

Pioglitazone

During controlled clinical trials, one case of overdose with pioglitazone was reported. A male patient took 120 mg per day for four days, then 100 mg per day for seven days. The patient denied any clinical symptoms during this period. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

Metformin hydrochloride

In the event of overdosage, supportive measures should be initiated. There are no specific antidotes. Supportive measures should include hospitalization of the patient and establishment of an adequate airway. The patient should be closely observed to determine the need for treatment with fluids, electrolytes, and hemodialysis. Hemodialysis may be useful in accelerating the excretion of metformin from the body.
Pioglitazone and metformin hydrochloride tablets, USP are a thiazolidinedione and biguanide combination product that contains two oral antidiabetic medications: pioglitazone hydrochloride and metformin hydrochloride.

Pioglitazone hydrochloride, USP is an odorless white crystalline powder that has a molecular formula of C19H17ClN3O3·HCl and a molecular weight of 382.80 dalton. It is soluble in 94%-dimethylformamide, slightly soluble in anhydrous ethanol, very slightly soluble in water and acetone, practically insoluble in ether, and insoluble in other solvents.

Metformin hydrochloride (N,N-dimethylformamidomethylcarbinylamine dihydrochloride), USP is a white crystalline powder with a molecular formula of C9H11ClN3O4·HCl and a molecular weight of 215.72. Metformin hydrochloride is freely soluble in water and is practically insoluble in ether, other, and chloroform. The pH of a 1% aqueous solution of metformin hydrochloride is 6.0. The structural formula is as shown.

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 agonistic for peroxisome proliferator-activated receptor-gamma (PPARγ). PPARγ receptors are found in tissues important for insulinization such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors mediates the transcription of a number of insulin responsive genes involved in control of glucose and lipid metabolism.

Because pioglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in insulin resistant individuals who lack endogenous insulin.

Medicinal Chemistry

Metformin hydrochloride improves glucose tolerance in patients with type 2 diabetes, lowering both fasting 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 is one of the most commonly used oral antidiabetic agents in patients with type 2 diabetes or as an oral hypoglycaemic agent in healthy subjects (except in specific circumstances, see Warnings and Precautions (5.4)) and does not cause hypoglycaemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pioglitazone and metformin hydrochloride tablets combine two antidiabetic medications with different mechanisms of action to improve glycaemic control in adults with type 2 diabetes: pioglitazone, a thiazolidinedione, and metformin, 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 agonistic for peroxisome proliferator-activated receptor-gamma (PPARγ). PPARγ receptors are found in tissues important for insulinization such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors mediates the transcription of a number of insulin responsive genes involved in control of glucose and lipid metabolism.

In animal models of diabetes, pioglitazone reduces the hyperglycaemia, hyperinsulinaemia, and hypertriglyceridaemia 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 insulin resistant models that lack endogenous insulin.

Medicinal Chemistry

Metformin hydrochloride improves glucose tolerance in patients with type 2 diabetes, lowering both fasting 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 is one of the most commonly used oral antidiabetic agents in patients with type 2 diabetes or as an oral hypoglycaemic agent in healthy subjects (except in specific circumstances, see Warnings and Precautions (5.4)) and does not cause hypoglycaemia. 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 glycaemic control when used in combination with a sulfonylurea, metformin, or insulin (see Clinical Studies (4.4)).

Patients with lipid abnormalities were included in the clinical trials with pioglitazone. Overall, patients treated with pioglitazone had mean decreases in triglyceride, insulin increases in HDL cholesterol, and no consistent mean changes in LDL and total cholesterol. There is no conclusive evidence of macrovascular benefits 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, multicenter 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 in a greater extent in patients treated with pioglitazone than in the placebo-treatment patients. There were no consistent differences for LDL and total cholesterol in patients treated with pioglitazone compared to placebo (see Table 16).

Table 15. Lipids in a 26-Week Placebo-Controlled Monotherapy Dose-Ranging Study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Triglycerides (mg/dL)</th>
<th>HDL Cholesterol (mg/dL)</th>
<th>LDL Cholesterol (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>N=79</td>
<td>123</td>
<td>N=67</td>
</tr>
<tr>
<td>Dose</td>
<td>N=62</td>
<td>256</td>
<td>N=62</td>
</tr>
<tr>
<td>Dose 15mg</td>
<td>N=63</td>
<td>256</td>
<td>N=63</td>
</tr>
<tr>
<td>Dose 30mg</td>
<td>N=63</td>
<td>256</td>
<td>N=63</td>
</tr>
<tr>
<td>Dose 45mg</td>
<td>N=63</td>
<td>256</td>
<td>N=63</td>
</tr>
</tbody>
</table>

Percent change from baseline (adjusted mean)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percent change from baseline (adjusted mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>-4.8%</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>+14.1%</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>-11.3%</td>
</tr>
</tbody>
</table>
In the two other monotherapy studies (16 weeks and 24 weeks) and in combination therapy studies with metformin (10 weeks and 24 weeks), the results were generally consistent with the data above.

### 12.3 Pharmacokinetics

**Absorption**

Pioglitazone and metformin hydrochloride tablets 15 mg/500 mg, and 30 mg/250 mg, are the area under the curve (AUC) and maximum concentration (Cmax) of both the pioglitazone and the metformin component following a single dose of the combination tablet were bioequivalent to pioglitazone 15 mg concomitantly administered with metformin hydrochloride tablets (500 mg or 850 mg respectively) under fasted conditions in healthy subjects.

Administration of pioglitazone and metformin hydrochloride tablets 15 mg/200 mg with food resulted in no change in overall exposure of pioglitazone. With metformin there was no change in AUC; however, mean peak serum concentrations of metformin was decreased by 28% when administered with food. A delayed time to peak serum concentration was observed for both components (3.5 hours for metformin and 0.8 hours for pioglitazone) under fed conditions. These changes are not likely to be clinically significant.

**Distribution**

**Pioglitazone**

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 500 mg to 2500 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an elimination in humans. 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 <3 mg/mL. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 mg/mL, even at maximum doses. Food decreases the rate and extent of metformin absorption, as shown by a 40% lower mean Cmax, a 29% lower AUC, and a 35-minute prolongation of T1/2, following administration of a single 500 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

**Metformin**

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 500 mg to 2500 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an elimination in humans. 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 <3 mg/mL. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 mg/mL, even at maximum doses. Food decreases the rate and extent of metformin absorption, as shown by a 40% lower mean Cmax, a 29% lower AUC, and a 35-minute prolongation of T1/2, following administration of a single 500 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

**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. Metabolites M-III and M-IV are the major circulating active metabolites in humans.

In vivo data demonstrate that multiple CYP isozymes are involved in the metabolism of pioglitazone whichinclude CYP2C8 and, to a lesser degree, CYP3A4 with additional contributions from a variety of other isozymes, including the mainly extrahepatic CYP1A1. In vivo study of pioglitazone in combination with gemfibrozil, a strong CYP3A4 inhibitor, showed that pioglitazone is a CYP3A4 substrate [see Drug Interactions (7.3)]. Urinary 6ß-hydroxycortisol/cortisol critical ratios measured in patients treated with pioglitazone showed the pioglitazone is not a strong CYP3A4 enzyme inhibitor.

**Metformin**

In patients with decreased renal function, the plasma and blood AUCs of metformin prolong and the renal clearance is decreased [see Drug Interactions (7.2)] of metformin and metformin tablets [see Warnings and Precautions (5.5)].

**Specific Populations**

**Renal Impairment**

**Pioglitazone**

The serum elimination half-life of pioglitazone, M-III and M-IV remain unchanged in patients with mild (Ccr = 30 to 50 mL/min) and severe (Ccr <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**

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

Pioglitazone

In healthy elderly subjects, Cmax of pioglitazone was not significantly different, but AUC values were approximately 21% higher than those achieved in younger subjects. The mean T1/2 of pioglitazone was also prolonged in elderly subjects (about 10 hours) as compared to younger subjects (about seven hours). These changes were not of a magnitude that would be considered clinically relevant.

Mechanism of Action

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total CL/F is decreased; the T1/2 is prolonged, and Cmax is increased, compared to healthy young subjects. From these data, it appears that the change in pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatrics

Safety and efficacy of pioglitazone in pediatric patients have not been established. Pioglitazone and metformin hydrochloride are not recommended for use in pediatric patients [see Use in Specific Populations (8.4)].

Mechanism of Action

After administration of a single oral metformin 500 mg tablet with food, geometric mean Cmax 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 Cmax and AUC values of pioglitazone were increased 20% to 60% in women compared to men in controlled clinical trials. HbA1c decreases from baseline were generally greater for females than for males (average mean difference in HbA1c 0.5%). Because therapy should be individualized for each patient to achieve glycemic control, no dose adjustment is recommended based on gender alone.

Mechanism of Action

Pioglitazone 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

Pharmacokinetic data among various ethnic groups are not available.

Mechanism of Action

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 Asians (n=40), Blacks (n=51), and Hispanics (n=24).

Drug-Drug Interactions

Specific pharmacokinetic drug interaction studies with pioglitazone and metformin hydrochloride tablets have not been performed, although such studies have been conducted with the individual components.

Table 18. Effect of Coadministered Drugs on Pioglitazone Systemic Exposure

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Name and Dose Regimen</th>
<th>Change in AUC*</th>
<th>Change in Cmax†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Contraceptives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levonorgestrel (LNG) 1 mg (N=24)</td>
<td>60 mg twice daily for 7 days</td>
<td>↑30%‡</td>
<td>0%</td>
</tr>
<tr>
<td>Ethinyl Estradiol (EE) 0.035 mg plus Norethindrone (NE) 1 mg for 21 days</td>
<td>5 mg twice daily for 7 days</td>
<td>↓30%</td>
<td>0%</td>
</tr>
<tr>
<td>Midazolam</td>
<td>10 mg (N=23)</td>
<td>↓31%‡</td>
<td>0%</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>75 mg single dose on Day 15</td>
<td>↓26%</td>
<td>0%</td>
</tr>
<tr>
<td>Nifedipine ER</td>
<td>30 mg daily for 7 days</td>
<td>↓14%</td>
<td>0%</td>
</tr>
<tr>
<td>Atenolol</td>
<td>100 mg single dose on Day 8</td>
<td>↓13%</td>
<td>0%</td>
</tr>
<tr>
<td>Theophylline</td>
<td>400 mg twice daily for 7 days</td>
<td>↓15%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 17. Effect of Pioglitazone Coadministration on Systemic Exposure of Other Drugs

<table>
<thead>
<tr>
<th>Pioglitazone Dosage Regimen (mg)§</th>
<th>Name and Dose Regimen</th>
<th>Change in AUC*</th>
<th>Change in Cmax†</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 mg (N = 12)</td>
<td>Daily loading then maintenance doses based on PT and INR values Quick's Value = 35 ± 5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45 mg (N = 12)</td>
<td>Daily loading then maintenance doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45 mg daily for 21 days (N = 35)</td>
<td>0.20 mg twice daily (loading dose) and 0.250 mg daily (maintenance dose, 7 days)</td>
<td>↓12%</td>
<td>11%</td>
</tr>
<tr>
<td>45 mg (N = 23)</td>
<td>5 mg twice daily for 7 days</td>
<td>↓30%</td>
<td>0%</td>
</tr>
<tr>
<td>45 mg daily for 8 days (N = 18)</td>
<td>5 mg daily for 7 days</td>
<td>↓13%</td>
<td>10%</td>
</tr>
<tr>
<td>45 mg daily for 4 days (N = 24)</td>
<td>5 mg twice daily for 7 days</td>
<td>↓30%</td>
<td>0%</td>
</tr>
<tr>
<td>45 mg daily for 4 days (N = 23)</td>
<td>5 mg twice daily for 7 days</td>
<td>↓30%</td>
<td>0%</td>
</tr>
<tr>
<td>45 mg daily for 2 days (N = 12)</td>
<td>5 mg single dose on Day 8</td>
<td>↓13%</td>
<td>0%</td>
</tr>
<tr>
<td>45 mg daily for 8 days (N = 24)</td>
<td>5 mg single dose on Day 15</td>
<td>↓13%</td>
<td>0%</td>
</tr>
<tr>
<td>45 mg daily for 7 days (N = 23)</td>
<td>5 mg single dose on Day 8</td>
<td>↓13%</td>
<td>0%</td>
</tr>
<tr>
<td>45 mg daily for 7 days (N = 12)</td>
<td>5 mg single dose on Day 15</td>
<td>↓13%</td>
<td>0%</td>
</tr>
<tr>
<td>45 mg daily for 4 days (N = 24)</td>
<td>5 mg single dose on Day 8</td>
<td>↓13%</td>
<td>0%</td>
</tr>
<tr>
<td>45 mg daily for 4 days (N = 23)</td>
<td>5 mg single dose on Day 8</td>
<td>↓13%</td>
<td>0%</td>
</tr>
<tr>
<td>45 mg daily for 2 days (N = 12)</td>
<td>5 mg single dose on Day 8</td>
<td>↓13%</td>
<td>0%</td>
</tr>
<tr>
<td>45 mg daily for 8 days (N = 24)</td>
<td>5 mg single dose on Day 15</td>
<td>↓13%</td>
<td>0%</td>
</tr>
<tr>
<td>45 mg daily for 7 days (N = 23)</td>
<td>5 mg single dose on Day 8</td>
<td>↓13%</td>
<td>0%</td>
</tr>
<tr>
<td>45 mg daily for 7 days (N = 12)</td>
<td>5 mg single dose on Day 15</td>
<td>↓13%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 19. Effect of Coadministered Drugs on Pioglitazone Systemic Exposure

<table>
<thead>
<tr>
<th>Coadministered Drug and Dose Regimen</th>
<th>Change in AUC*</th>
<th>Change in Cmax†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin 600 mg twice daily for 2 days (N = 12)</td>
<td>↓16%</td>
<td>0%</td>
</tr>
<tr>
<td>Atorvastatin 20 mg twice daily for 7 days (N = 21)</td>
<td>↓14%</td>
<td>0%</td>
</tr>
<tr>
<td>Rifampin 600 mg daily for 3 days (N = 10)</td>
<td>↓14%</td>
<td>0%</td>
</tr>
<tr>
<td>Fosphenytoin 60 mg twice daily for 7 days (N = 23)</td>
<td>↓14%</td>
<td>0%</td>
</tr>
<tr>
<td>Ramipril 5 mg twice daily for 4 days (N = 23)</td>
<td>↓14%</td>
<td>0%</td>
</tr>
<tr>
<td>Nifedipine ER 30 mg daily for 7 days (N = 23)</td>
<td>↓14%</td>
<td>0%</td>
</tr>
<tr>
<td>Atenolol 50 mg daily for 7 days (N = 23)</td>
<td>↓14%</td>
<td>0%</td>
</tr>
<tr>
<td>Theophylline 400 mg twice daily for 7 days (N = 23)</td>
<td>↓14%</td>
<td>0%</td>
</tr>
<tr>
<td>Tiotropium 96 mg twice daily for 7 days§</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
### Table 19. Effect of Concomitantly Administered Drug on Plasma Metformin Systemic Exposure

<table>
<thead>
<tr>
<th>Concomitantly Administered Drug</th>
<th>Glyburide</th>
<th>Furosemide</th>
<th>Nifedipine</th>
<th>Propafenone</th>
<th>Suprofen</th>
<th>Glyburide</th>
<th>Furosemide</th>
<th>Nifedipine</th>
<th>Propafenone</th>
<th>Suprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose of Metformin*</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
</tr>
<tr>
<td>Geometric Mean Ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 20. Effect of Metformin on Plasma Metformin Systemic Exposure

<table>
<thead>
<tr>
<th>Concomitantly Administered Drug</th>
<th>Glyburide</th>
<th>Furosemide</th>
<th>Nifedipine</th>
<th>Propafenone</th>
<th>Suprofen</th>
<th>Glyburide</th>
<th>Furosemide</th>
<th>Nifedipine</th>
<th>Propafenone</th>
<th>Suprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose of Metformin*</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
</tr>
<tr>
<td>Geometric Mean Ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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 tablets 15/850 mg, pioglitazone 15 mg or metformin 850 mg twice daily. Statistically significant improvements in HbA1c and fasting plasma glucose (FPG) were observed in patients treated with pioglitazone and metformin hydrochloride tablets compared to either pioglitazone or metformin alone (see Table 21).

### Table 21 Glycemic Parameters in 24-Week Study of Pioglitazone and Metformin Hydrochloride Tablets in Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Diet and Exercise Alone

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Pioglitazone and Metformin Hydrochloride Tablets</th>
<th>Pioglitazone 15 mg</th>
<th>Metformin 850 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>N=185</td>
<td>N=162</td>
<td>N=193</td>
</tr>
<tr>
<td>Baseline</td>
<td>8.7</td>
<td>8.7</td>
<td>8.7</td>
</tr>
<tr>
<td>Change from Baseline (adjusted mean)*</td>
<td>-1.6</td>
<td>-1.0</td>
<td>-0.8</td>
</tr>
</tbody>
</table>

*Change from Baseline is calculated as pioglitazone and metformin hydrochloride tablets (adjusted mean) minus pioglitazone and metformin hydrochloride tablets (baseline) minus metformin 850 mg (baseline).
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 tablets with coadministered pioglitazone and metformin tablets 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 monotherapy with metformin, either alone or in combination with another antilipidemic agent. All other antilipidemic agents were withdrawn at least three weeks prior to starting study treatment.

In the first trial, 328 patients were randomized to receive either 30 mg of pioglitazone or placebo once daily for 24 weeks in addition to their current metformin regimen. Treatment with pioglitazone as add-on to metformin produced statistically significant improvements in HbA1c and FPG at endpoint compared to placebo add-on to metformin (see Table 22).

| Table 22. Glycemic Parameters in a 26-Week Placebo-Controlled, Add-on to Metformin Trial
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Baseline (mean)</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
</tr>
<tr>
<td>Baseline (mean)</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
</tr>
</tbody>
</table>

In the second trial, 827 patients were randomized to receive either 30 mg or 45 mg of pioglitazone once daily for 24 weeks in addition to their current metformin regimen. The mean reduction from baseline at Week 24 in HbA1c was 0.8% for the 30 mg dose and 1.0% for the 45 mg dose (see Table 22). The mean reduction from baseline at Week 24 in FPG was 38 mg/dL for the 30 mg dose and 51 mg/dL for the 45 mg dose.

**Table 23. Glycemic Parameters in a 26-Week Add-on to Metformin Study**

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>Pioglitazone 30 mg + Metformin</th>
<th>Pioglitazone 45 mg + Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (mean)</td>
<td>9.9</td>
<td>9.9</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>9.9</td>
<td>9.9</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
</tbody>
</table>

**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 tablets as follows:

- 15 mg/500 mg tablet: white to off-white, colored, capsule shaped, bi-convex, film coated tablets blistered with "15/500" on one side and "5/1280" on other side, available in:
  - Bottles of 60 NDC: 13668-280-60
  - Bottles of 180 NDC: 13668-280-33
  - Bottles of 500 NDC: 13668-280-05
  - Bottles of 1000 NDC: 13668-280-10

- 15 mg/500 mg tablet: white to off-white, colored, capsule shaped, bi-convex, film coated tablets blistered with "15/500" on one side and "5/1280" on other side, available in:
  - Bottles of 60 NDC: 13668-281-60
  - Bottles of 180 NDC: 13668-281-33
  - Bottles of 500 NDC: 13668-281-05
  - Bottles of 750 NDC: 13668-281-10

**Storage**: Store at 20° to 25°C (68° to 77°F). Excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Keep container tightly closed, and protect from moisture.

**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 glycated 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 signs of macroscopic hematuria or other symptom such as dysuria or urgency that develop or increase during treatment as these may be due to bladder cancer.
- Explain to patients the risk of lactic acidosis, its symptoms and condition that predispose to its development, as noted in the Warnings and Precautions (5.2) section. Advise patients to discontinue pioglitazone and metformin hydrochloride tablets immediately and to promptly notify their healthcare professional if unplanned hyperventilation, myalgia, gastrointestinal symptoms, malaise, unusual somnolence, or other nonspecific symptoms occur. Instruct patients in the necessity for discontinuation of pioglitazone and metformin hydrochloride tablets prior to any surgical or radiological procedure, as temporary discontinuation of pioglitazone and metformin hydrochloride tablets may be required until renal function has been confirmed to be normal.
- Counsel patients against excessive alcohol intake while receiving pioglitazone and metformin hydrochloride tablets.
- Inform patients to immediately report symptoms of an unusually rapid increase in weight or edema, shortness of breath, or any other symptoms of heart failure while receiving pioglitazone and metformin hydrochloride tablets.
- Tell patients to promptly stop taking pioglitazone and metformin hydrochloride tablets 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 hemogramic parameters.
When receiving treatment with pioglitazone and metformin hydrochloride tablets,

- Inform female patients that treatment with pioglitazone and metformin hydrochloride tablets may result in an increased pregnancy risk in premenopausal anovulatory females due to its effect on ovulation [see Use in Specific Populations (8.5)].

- Patients should be advised to notify their health practitioner or call the Poison Control Center immediately in case of pioglitazone and metformin hydrochloride tablets overdose.

- Combination antidiabetic therapy may cause hypoglycemia. When instituting pioglitazone and metformin hydrochloride tablets, the risks of hypoglycemia, its symptoms and treatment, and conditions predisposing to its development should be explained to patients and their family members.

- Patients should be told to take pioglitazone and metformin hydrochloride tablets as prescribed and instructed that any change in dosage should only be done by their physician. If a dose is missed on one day, the dose should not be doubled the following day.

Manufactured by:
TORRENT PHARMACEUTICALS LTD., Indrani-382 721,
Dist. Mehsana, INDIA.

For:
TORRENT PHARMA INC.,
130 Allen Road, Suite 102
Raritan Ridge, NJ 07920.

1997/0001

Revised January 2018

SPL MEDGUIDE

MEDICATION GUIDE

PIOGLITAZONE AND METFORMIN HYDROCHLORIDE (PYE o GLI ta zone and met FOR min HYE-droe-KLOR-ide) TABLETS, USP

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

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

Pioglitazone and metformin hydrochloride tablets can cause serious side effects, including:

- new or worse heart failure: Pioglitazone, one of the medicines in pioglitazone and metformin hydrochloride tablets, can cause your body to keep extra fluid (fluid retention), which leads to swelling (edema) and weight gain. Extra body fluid can make some heart problems worse or lead to heart failure. Heart failure means your heart does not pump blood well enough.

- Do not take pioglitazone and metformin hydrochloride tablets if you have severe heart failure.

- If you have heart failure with symptoms (such as shortness of breath or swelling), even if these symptoms are not severe, pioglitazone and metformin hydrochloride tablets may not be right for you.

Call your doctor right away if you have any of the following:

- swelling or fluid retention, especially in the ankles or legs
- shortness of breath or trouble breathing, especially when you lie down
- an unusually fast increase in weight
- unusual tiredness

- lactic acidosis. Metformin, one of the medicines in pioglitazone and metformin hydrochloride tablets, can cause a rare but serious condition called lactic acidosis (a build up of an acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

- Call your doctor right away if you have any of the following symptoms, which could be signs of lactic acidosis:

  - you feel cold in your hands or feet
  - you feel dizzy or lightheaded
  - you have a slow or irregular heartbeat
  - you feel very weak or tired
  - you have trouble breathing
  - you feel sleepy or drowsy
  - you have vomiting, nausea, or warning.

- Patients who have had lactic acidosis with metformin have other things that, combined with the metformin, led to the lactic acidosis. Tell your doctor if you have any of the following, because you may have a higher chance of getting lactic acidosis with pioglitazone and metformin hydrochloride tablets:

  - have severe kidney problems or your kidneys are affected by certain x-ray tests that use injectable dye. have liver problems
  - have severe heart failure
  - use alcohol very often, or drink a lot of alcohol in short-term "binge" drinking and do not drink enough fluids
  - have surgery
  - have a heart attack, severe infection, or stroke

The best way to keep from having a problem with lactic acidosis from metformin is to stop taking metformin if you have any of the problems listed above. Your doctor may decide to stop your pioglitazone and metformin hydrochloride tablets for a while if you have any of these things:

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

What are the possible side effects of pioglitazone and metformin hydrochloride tablets?

Pioglitazone and metformin hydrochloride tablets contain two prescription diabetes medicines called pioglitazone and metformin hydrochloride. Pioglitazone and metformin hydrochloride tablets can cause swelling (fluid retention), which leads to weight gain. Pioglitazone and metformin hydrochloride tablets are not for people with type 1 diabetes. Pioglitazone and metformin hydrochloride tablets are not for people with diabetes lactic acidosis (increased lactic acid in your blood or urine).

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

Who should not take pioglitazone and metformin hydrochloride tablets?

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

Do not take pioglitazone and metformin hydrochloride tablets if you:

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

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

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

Before you take pioglitazone and metformin hydrochloride tablets, tell your doctor if your...
What are the ingredients in pioglitazone and metformin hydrochloride tablets? If you would like more information, talk with your doctor. You can ask your pharmacist or other health care professional if you are not sure.

This Medication Guide summarizes the most important information about pioglitazone and metformin hydrochloride tablets. It does not list all the possible side effects of pioglitazone and metformin hydrochloride tablets. This can increase your chance of getting pregnant. 

If you are pregnant or plan to become pregnant. Talk to your doctor about the best way to control your blood glucose levels while breastfeeding. 

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

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

How should I take pioglitazone and metformin hydrochloride tablets? Take pioglitazone and metformin hydrochloride tablets exactly as your doctor tells you to take them. Your doctor may need to change your dose of pioglitazone and metformin hydrochloride tablets. Do not change your dose of pioglitazone and metformin hydrochloride tablets without talking to your doctor. 

Pioglitazone and metformin hydrochloride tablets may be prescribed alone or with other diabetes medicines. This will depend on how well your blood sugar is controlled. 

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

Stay on your diet and exercise programs and test your blood sugar regularly while taking pioglitazone and metformin hydrochloride tablets. 

What are the possible side effects of pioglitazone and metformin hydrochloride tablets? Pioglitazone and metformin hydrochloride tablets may cause serious side effects, including:

- See "What is the most important information I should know about pioglitazone and metformin hydrochloride tablets?" 
- low blood sugar (hypoglycemia). This can happen if you skip meals, if you also use another medicine that lowers blood sugar, or if you have certain medical problems. Lightheadedness, dizziness, shakiness, or hunger may happen if your blood sugar is too low. Call your doctor if low blood sugar levels are a problem for you. 
- The most common side effects of pioglitazone and metformin hydrochloride tablets include:
  - cold-like symptoms (upper respiratory tract infection)
  - swelling (edema)
  - diarrhea
  - headache
  - increased weight

Tell your doctor if you have any side effect that bother you or that does not go away. There are not all the side effects of pioglitazone and metformin hydrochloride tablets. For more information, ask your doctor or pharmacist. 

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

How should I store pioglitazone and metformin hydrochloride tablets? 

- Keep pioglitazone and metformin hydrochloride tablets in a cool place, not frozen, and out of direct sunlight. 
- Keep the pioglitazone and metformin hydrochloride tablets bottle tightly closed and keep tablets dry. 

Keep the pioglitazone and metformin hydrochloride tablets bottle tightly closed and keep tablets dry. 

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

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

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use pioglitazone and metformin hydrochloride tablets for a condition for which it was not prescribed. 

Do not give pioglitazone and metformin hydrochloride tablets to other people, even if they have the same symptoms you have. It may harm them. 

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

For more information call 1-800-812-8887. 

What are the ingredients in pioglitazone and metformin hydrochloride tablets?
Active Ingredients: pioglitazone hydrochloride, USP and metformin hydrochloride, USP

Inactive Ingredients: croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, and titanium dioxide

Trademarks are the property of their respective owners.

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

Licensed - United States Patents Nos. 5,965,384, 6,166,042, 6,166,043, and 6,172,090.

Manufactured by:
TORRENT PHARMACEUTICALS LTD., Indrad-382 721,
Dist. Mehsana, INDIA.

For:
TORRENT PHARMA INC.
150 Allen Road, Suite 102
Basking Ridge, NJ 07920

Revised January 2018

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL
Pioglitazone and Metformin Hydrochloride Tablets - 15 mg / 500 mg

Pioglitazone and Metformin Hydrochloride Tablets - 15 mg / 850 mg

Pioglitazone HCL AND METFORMIN HCL
pioglitazone hcl and metformin hcl tablet
Product Information

Product Type
HUMAN PRESCRIPTION DRUG

Item Code (Source)
NDC:13668-281

Route of Administration
ORAL

Active Ingredient/Active Moiety

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>METFORMIN HYDROCHLORIDE (UNII: 786Z46389E)</td>
<td>METFORMIN HYDROCHLORIDE</td>
<td>500 mg</td>
</tr>
<tr>
<td>PIOGLITAZONE HYDROCHLORIDE (UNII: JQT35NPK6C)</td>
<td>PIOGLITAZONE HYDROCHLORIDE</td>
<td>15 mg</td>
</tr>
</tbody>
</table>

Inactive Ingredients

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>CELLULOSE, MICROCRYSTALLINE (UNII: 0P1R32D61U)</td>
<td></td>
</tr>
<tr>
<td>CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)</td>
<td></td>
</tr>
<tr>
<td>HYDROXYPROPYLMETHYLCELLULOSE (UNII: 50Y2UAC39Q)</td>
<td></td>
</tr>
<tr>
<td>MICROCRYSTALLINE CELLULOSE (UNII: 0WZ8WG20P6)</td>
<td></td>
</tr>
<tr>
<td>MAGNESIUM STEARATE (UNII: 70097M6I30)</td>
<td></td>
</tr>
<tr>
<td>POLYETHYLENE GLYCOL 8000 (UNII: Q662QK8M3B)</td>
<td></td>
</tr>
<tr>
<td>POVIDONE K30 (UNII: U725QWY32X)</td>
<td></td>
</tr>
<tr>
<td>TALC (UNII: 7SEV7J4R1U)</td>
<td></td>
</tr>
<tr>
<td>TITANIUM DIOXIDE (UNII: 15FIX9V2JP)</td>
<td></td>
</tr>
</tbody>
</table>

Product Characteristics

<table>
<thead>
<tr>
<th>Color</th>
<th>Shape</th>
<th>Size</th>
<th>Flavor</th>
<th>Imprint Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHITE</td>
<td>CAPSULE</td>
<td>14mm</td>
<td></td>
<td>1280</td>
</tr>
</tbody>
</table>

Packaging

<table>
<thead>
<tr>
<th>#</th>
<th>Item Code</th>
<th>Package Description</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NDC:13668-280-06</td>
<td>500 Tablets</td>
<td>REVISED 02/13/2013</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>NDC:13668-280-33</td>
<td>180 Tablets</td>
<td>REVISED 02/13/2013</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>NDC:13668-280-05</td>
<td>500 Tablets</td>
<td>REVISED 02/13/2013</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>NDC:13668-280-10</td>
<td>1000 Tablets</td>
<td>REVISED 02/13/2013</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>NDC:13668-280-74</td>
<td>100 Tablets</td>
<td>REVISED 02/13/2013</td>
<td></td>
</tr>
</tbody>
</table>

Marketing Information

<table>
<thead>
<tr>
<th>Marketing Category</th>
<th>Application Number or Monograph Citation</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANDA</td>
<td>ANDA202001</td>
<td>02/13/2013</td>
<td>02/13/2013</td>
</tr>
</tbody>
</table>


PROGLITAZONE HCL AND METFORMIN HCL
pioglitazone hcl and metformin hcl tablet
Product Information

Product Type
HUMAN PRESCRIPTION DRUG

Item Code (Source)
NDC:13668-280
## Active Ingredient/Active Moiety

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>METFORMIN HYDROCHLORIDE (UNII: 786Z46389E)</td>
<td>METFORMIN -</td>
<td>850 mg</td>
</tr>
<tr>
<td>PIOGLITAZONE HYDROCHLORIDE (UNII: JQT35NPK6C)</td>
<td>PIOGLITAZONE -</td>
<td>15 mg</td>
</tr>
</tbody>
</table>

## Inactive Ingredients

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)</td>
<td></td>
</tr>
<tr>
<td>CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)</td>
<td></td>
</tr>
<tr>
<td>HYPROMELLOSE 2910 (6 MPA.S) (UNII: 0WZ8WG20P6)</td>
<td></td>
</tr>
<tr>
<td>MAGNESIUM STEARATE (UNII: 70097M6I30)</td>
<td></td>
</tr>
<tr>
<td>POLYETHYLENE GLYCOL 8000 (UNII: Q662QK8M3B)</td>
<td></td>
</tr>
<tr>
<td>POVIDONE K30 (UNII: U725QWY32X)</td>
<td></td>
</tr>
<tr>
<td>TALC (UNII: 7SEV7J4R1U)</td>
<td></td>
</tr>
<tr>
<td>TITANIUM DIOXIDE (UNII: 15FIX9V2JP)</td>
<td></td>
</tr>
</tbody>
</table>

## Product Characteristics

<table>
<thead>
<tr>
<th>Color</th>
<th>Shape</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHITE (white to off-white)</td>
<td>CAPSULE</td>
<td>18mm</td>
</tr>
</tbody>
</table>

## Packaging

<table>
<thead>
<tr>
<th>#</th>
<th>Item Code</th>
<th>Package Description</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NDC:13668-281-05</td>
<td>500 in 1 BOTTLE, Type: No a Combination Product</td>
<td>02/13/2013</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>NDC:13668-281-09</td>
<td>750 in 1 BOTTLE, Type: No a Combination Product</td>
<td>02/13/2013</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>NDC:13668-281-12</td>
<td>100 in 1 CARTON, Type: No a Combination Product</td>
<td>02/13/2013</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>NDC:13668-281-60</td>
<td>60 in 1 BOTTLE, Type: No a Combination Product</td>
<td>02/13/2013</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>NDC:13668-281-33</td>
<td>180 in 1 BOTTLE, Type: No a Combination Product</td>
<td>02/13/2013</td>
<td></td>
</tr>
</tbody>
</table>

## Marketing Information

<table>
<thead>
<tr>
<th>Market Category</th>
<th>Application Number or Monograph Citation</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANDA</td>
<td>ANDA202001</td>
<td>02/13/2013</td>
<td></td>
</tr>
</tbody>
</table>

## Labeler

- **Labeler**: Torrent Pharmaceuticals Limited (916488547)

## Registrant

- **Registrant**: Torrent Pharma, Inc. (790033935)

## Establishment

<table>
<thead>
<tr>
<th>Name</th>
<th>Address</th>
<th>EIN</th>
<th>Business Operations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Torrent Pharmaceuticals Limited</td>
</tr>
</tbody>
</table>

*Revised: 2/2019*