

(45 mg of pioglitazone and 2,550 mg of metformin HC). Total daily dosages of 2,550 mg of metformin HCl may be taken in divided doses three times a day to reduce gastrointestinal adverse reactions [see Adverse Reactions (6.1)].

Pioglitazone and metformin hydrochloride tablets are contraindicated in patients with an estimated glomerular filtration rate (eGFF

Initiation of pioglitazone and metformin hydrochloride tablets in patients with an eGFR between 30 to 45 mL/min is not recommended.

hydrochloride tablets is 15 mg of pioglitazone and 850 mg of metformin [see Boxed Warning and Warnings and Precautions (5. 1)].

related to fluid retention as has been seen with pioglitazone (e.g., weight gain, edema and signs and symptoms of congestive heart failure).

Established NYHA Class III or IV heart failure at the time of pioglitazone and metformin hydrochloride tablets initiation Isee Boxed

Pioglitazone, like other thiazolidinediones, can cause dose-related fluid retention when used alone or in combination with other antidiabetic

pioglitazone and metformin hydrochloride tablets, consider discontinuation of pioglitazone and metformin hydrochloride tablets or dosage

rment (e.g., the elderly), renal function should be assessed more fre

Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis

tients with hepatic impairment have developed with cases of metformin-associated lactic acidosis. This may be due to impaired lactate

In controlled clinical trials with pioglitazone, edema was reported more frequently in patients treated with pioglitazone than in placebo-treated

patients and is dose related [see Adverse Reactions (6.1)]. In postmarketing experience, reports of new onset or worsening of edema have

Pioglitazone and metformin hydrochloride should be used with caution in patients with edema. Because thiazolidinediones, including

Insulin and insulin secretagogues, such as sulfonylureas, are known to cause hypoglycemia. Therefore, a lower dosage of insulin or

nere have been postmarketing reports of fatal and non-fatal hepatic failure in patients taking pioglitazone, although the reports conta

insufficient information necessary to establish the probable cause. There has been no evidence of drug-induced hepatotoxicity in the

Patients with type 2 diabetes mellitus may have fatty liver disease or cardiac disease with episodic congestive heart failure, both of which may cause liver test abnormalities, and they may also have other forms of liver disease, many of which can be treated or managed. Therefore, obtaining a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total

bilirubin) and assessing the patient is recommended before initiating pioglitazone and metformin hydrochloride therapy. In patients with

discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have clinically significant liver enzyme elevations (serum

LT greater than three times the ULN) and if abnormal liver tests persist or worsen, pioglitazone and metformin hydrochloride should be

nors were observed in the urinary bladder of male rats in the two year carcinogenicity study *[see Nonclinical Toxicology (13.1)]*. In

tion, during the three year PROactive clinical trial, 14 patients out of 2,605 (0.54%) randomized to pioglitazone and 5 out of 2,633

(0.19%) randomized to placebo were diagnosed with bladder cancer. After excluding patients in whom exposure to study drug was less

than one year at the time of diagnosis of bladder cancer, there were 6 (0.23%) cases on pioglitazone and 2 (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

A large prospective 10 year observational cohort study conducted in the United States (U.S) found no statistically significant increase in the

A retrospective cohort study conducted with data from the United Kingdom found a statistically significant association between eve

studies including the 10 year observational study in the U.S., but were in others. Inconsistent findings and limitations inherent in these and

Pioglitazone may be associated with an increase in the risk of urinary bladder tumors. There are insufficient data to determine whether

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 PROactive (the Prospective Pioglitazone Clinical Trial in Macrovascular Events). 5,238 patients with type 2 diabetes mellitus and a history

In the dark (the tropped to the dark in the tropped to the tropped to the dark in the tropped to the dark in the tropped to the dark in the tropped to the

versus 2.5% (23/905) for placebo. This difference was noted after the first year of treatment and persisted during the course of the study. The

majority of fractures observed in female patients were nonvertebral fractures including lower limb and distal upper limb. No increase in the incidence of fracture was observed in men treated with pioglitazone (1.7%) versus placebo (2.1%). The risk of fracture should be considered

in the care of patients, especially female patients, treated with pioglitazone and metformin hydrochloride and attention should be given to

Some patients presented with blurred vision or decreased visual acuity, but others were diagnosed on routine ophthalmologic examination.

Most patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after

lar edema has been reported in postmarketing experience in diabetic patients who were taking pioglitazone or another thiazolidinedion

risk of bladder cancer in diabetic patients ever exposed to pioglitazone, compared to those never exposed to pioglitazone [HR = 1.06; (95%

nized to pioglitazone or placebo [Hazard Ratio (HR) = 1.00; (95% Confidence Interval (CI): 0.59, 1.72)].

interrupted and investigation done to establish the probable cause. Pioglitazone and metformin hydrochloride should not be restarted in these

re liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal

hould be monitored for signs and symptoms of congestive heart failure [see Boxed Warning, Warnings and Precautions (5.1)].

Warn patients against excessive alcohol intake while receiving pioglitazone and metformin hydrochloride tablets.

s renal function prior to initiation of pioglitazone and metformin hydrochloride tablets and periodically thereafter [see Use ii

DIMENSIONS (MM) ART WORK SIZE DATE

PRODUCT NAME ITEM / PACK DESIGN STYLE

CODE

ADVERSE REACTIONS In patients taking pioglitazone and metformin hydrochloride tablets whose eGFR later falls below Discontinue pioplitazone and metformin hydrochloride tablets if the patient's eGFR later falls below 30 mL/min *Isee Contraindications* Fractures [see Warnings and Precautions (5.7)] Starting Dosage in Patients with NYHA Class I or II Congestive Heart Failure For patients with preexisting NYHA Class I or II congestive heart failure, the recommended starting dosage of pioglitazone and metformin 6.1 Clinical Trials Experience

pper Respiratory 1 leadache Sinusitis Myalgia



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 HCI is dialyzable, with a clearance of up to 170 mL/min under good hemodynamic conditions).

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 Upper Respiratory Pioglitazone and metformin hydrochloride tablets are contraindicated in patients with an eGFR less than 30 mL/min. Initiation Edema of pioglitazone and metformin hydrochloride tablets is not recommended in patients with eGFR between 30 to 45 mL/min [see • Obtain an eGFB at least annually in all patients taking pioplitazone and metformin hydrochloride tablets. In patients at increased risk for Weight Increased

- In patients taking pioolitazone and metformin hydrochloride tablets whose eGFR later falls below 45 mL/min, assess the benefit and risk. term of "edema." acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation (e.g., cationic drugs) [see Drug Interactions (7)]. Therefore, consider more frequent monitoring of patients. Administered Twice Daily ssociated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of havin hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients [see Use in Specific Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop pioplitazone and metformin hydrochloride tables at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Diarrhea
- Re-evaluate eGFR 48 hours after the imaging procedure, and restart pioglitazone and metformin hydrochloride tablets if renal function is Headache In this 24 week trial pioglitazone monotherapy group and 3.3% in the metformin monotherapy group Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. Pioglitazone and metformin hydrochloride tablets should be temporarily discontinued while patients have restricted food and Common Adverse Events: PROactive Trial who received placebo. Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such
- ypoglycem Edema clearance resulting in higher lactate blood levels. Therefore, avoid use of pioglitazone and metformin hydrochloride tablets in patients with Cardiac Failure Pain in Extremit
 - Chest Pair Mean duration of patient follow-up was 34.5 month

to Metformi

At least one congest heart failure event Table 7: Treatment-E Patients Treated wi

Findings regarding the risk of bladder cancer in patients exposed to pioglitazone vary among observational studies; some did not find an At least one conneart failure event

At least one conheart failure event ospitalized

Patients Treated wit

HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use PIOGLITAZONE AND METFORMIN HYDROCHLORIDE TABLETS safely and effectively. See full prescribing information for PIOGLITAZONE AND METFORMIN HYDROCHLORIDE TABLETS. PIOGLITAZONE AND METFORMIN HYDROCHLORIDE Tablets, for oral use Initial U.S. Approval: 2005

- WARNING: CONGESTIVE HEART FAILURE and LACTIC ACIDOSIS See full prescribing information for complete boxed warning. Congestive Heart Failure Thiazolidinediones, including pioglitazone, which is a component of pioglitazone and metformin hydrochloride tablets, cause or exacerbate congestive heart failure in some patients. (5.1) After initiation of pioglitazone and metformin hydrochloride tablets, and after dose increases, monitor patients carefully
- for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea, and/or edema). If congestive heart failure develops while taking pioglitazone and netformin hydrochloride tablets, consider discontinua pioglitazone and metformin hydrochloride tablets or dosage reduction of pioglitazone in pioglitazone and metformin hydrochloride tablets. (5.1) Pioglitazone and metformin hydrochloride tablets are not
- commended in patients with symptomatic heart failure. (5.1) Initiation of pioplitazone and metformin hydrochloride tablets in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated. (4, 5.1) actic Acidosis Postmarketing cases of metformin-associated lactic acidosis

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Pioglitazone and

Metformin

Hydrochloride Tablets

08099813

- have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate:pyruvate ratio; and metformin plasma levels generally greater than 5 mcg/mL. (5.2)
- Risk factors include renal impairment, concomitant use of certain drugs, age ${\geq}65$ years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high-risk groups are provided in the Full rescribing Information. (5.2) If lactic acidosis is suspected, discontinue pioulitazone and metformin hydrochloride tablets and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.2)
- --- RECENT MAJOR CHANGES --Dosage and Administration Dosage and Administration Important Dosage and Administration Information (2.1)06/2024 Most common adverse reactions (>5%) are upper respiratory tract 5.1 Congestive Heart Failure ations for Use in Patients with Renal Impairment (2.3).....

Coadministration with Strong CYP2C8 Inhibitors (2.5)....... 06/2024 www.fda.gov/medwatch. ----- INDICATIONS AND USAGE -----proliferator receptor gamma, and metformin hydrochloride (HCl), a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1) imitations of Use

Not recommended for treatment of type 1 diabetes or diabetic ketoacidosis. (1) ----- DOSAGE AND ADMINISTRATION ----

- Obtain liver tests before initiation. If abnormal, use caution when • Alcohol: Warn patients against excessive alcohol intake. (7.5) investigate the probable cause, treat (if possible), and follow appropriately, (2,1)
- reactions with metformin (2.1) regimen and titrate the dosage gradually, as needed after assessing therapeutic response and tolerability. The maximum recommendational tend led Individualize the starting dose based on the patient's current
- Prior to initiation, assess renal function with estimated impairment. (8.7) glomerular filtration rate (eGFR). (2.2) Contraindicated in patients with eGFR below 30 mL/min Guide
- Initiation is not recommended in patients with eGFR between 30 to 45 mL/min Assess risk/benefit of continuing pioglitazone and metformin wdrochloride tablets if eGFR falls below 45 ml /m Discontinue if eGFR falls below 30 mL/min

FULL PRESCRIBING INFORMATION: CONTENTS* WARNING: ESTIVE HEART FAILURE and LACTIC ACIDOSIS 1 INDICATIONS AND USAGE

- 2 DOSAGE AND ADMINISTRATION Important Dosage and Administration Information
- Recommended Dosage and Administration 2.3 Recommendations for Use in Patients with Renal
- Impairment 2.4 Recommendations for Congestive Heart Failure Coadministration with Strong CYP2C8 Inhibitors
- 2.6 Discontinuation for Iodinated Contrast Imaging Procedures 3 DOSAGE FORMS AND STRENGTHS
- **4** CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS Congestive Heart Failure
- 5.2 Lactic Acidosis 5.3 Edema 5.4 Hypoglycemia with Conco
- Insulin Secretagogues 5.5 Hepatic Effects
- 5.6 Urinary Bladder Tumors Fractures
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- Strong CYP2C8 Inhibitors 7.2 CYP2C8 Inducers
- Carbonic Anhydrase Inhibitors 7.4 Drugs that Reduce Metformin Clearance
- FULL PRESCRIBING INFORMATION WARNING: CONGESTIVE HEART FAILURE and LACTIC ACIDOSIS Connective Heart Failure Thiazolidinediones, including pioglitazone, which is a component of 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., excessive, rapid weight gain, dyspnea, and/or edema). If congestive heart failure
- Precautions (5.1)] Pioglitazone and metformin hydrochloride tablets are not recommended in patients with symptomatic 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), Warnings and Precautions (5.1)]. Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant
- bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific toms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-asso acidosis was characterized by elevated blood lactate levels (greater than 5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate:pyruvate ratio; and metformin plasma levels generally greater than 5 mcg/mL [see Warnings and Precautions (5.2)]. Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment
- Interactions (7). 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 glitazone and metformin hydrochloride tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Limitations of Use ioglitazone and metformin hydrochloride tablets are not recommended to treat type 1 diabetes mellitus or diabetic ketoacidosis.
- 2 DOSAGE AND ADMINISTRATION
- 2.1 Important Dosage and Administration Information Obtain liver tests (serum alanine and aspartate aminotransferases, alkaline phosphatase, and total bilirubin) prior to initiating pioglitazone and metformin hydrochloride tablets [see Warnings and Precautions (5.5)]. Proglitazone and metformin hydrochloride tablets contains 15 mg of pioglitazone and 500 mg of metformin hydrochloride (HCl) and 15 mg of pioglitazone and 850 mg of metformin hydrochloride (HCl) in each tablet. Associations between cumulative dose or cumulative duration of exposure to pioglitazone and bladder cancer were not detected in som studies including the 10 year observational study in the U.S., but were in others. Inconsistent findings and limitations inherent in these and studies including the 10 year observational study in the U.S., but were in others. Inconsistent findings and limitations inherent in these and studies including the 10 year observational study in the U.S., but were in others.
- Take pioglitazone and metformin hydrochloride tablets with meals to reduce gastrointestinal adverse reactions with metformin [see dotter studies preclude conclusive interpretations of the observational data. If a dose is missed, do not double the next dose 2.2 Recommended Dosage and Administration
- Recommended Starting Dosage Based on Current Regimen Individualize the starting dosage of pioglitazone and metformin hydrochloride tablets based on the patient's current regimen and the available strength of pioglitazone and metformin hydrochloride tablets (see Table 1).
- Table 1: Recommended Starting Dosage Based on the Patient's Current Regime Starting Dosage of pioglitazone and metformin hydrochloride Current Regimen tablets (15 mg of pioglitazone and 850 mg of metformin HCl per tablet)* One tablet orally once daily Not treated with either pioglitazone or metformin HCI Metformin HC One tablet orally once or twice daily. Select a dosage that is as close as possible to the current dosage of metformin HCI Pioglitazone One tablet orally once daily Select a dosage that is as close as possible to the current dosage Pioglitazone and metformin H0 of pioglitazone and metformin HCI while not exceeding three

tablets orally per day. *For dosage recommendations for patients with renal impairment and/or congestive heart failure, see Dosage and Administration (2.3, 2.4,

initiation and dose increases. (2.4) Pioglitazone and metformin hydrochloride tablets may need to be tolerability. discontinued at time of, or prior to, iodinated contrast imaging | Pioglitazone and metformin hydrochloride tablets may be increased to a maximum recommended total daily dosage of three tablets per day 5.9 Vitamin B₁₂ Levels procedures. (2.6) ----- DOSAGE FORMS AND STRENGTHS --Tablets: 15 mg pioglitazone /500 mg metformin hydrochloride and 2.3 Recommendations for Use in Patients with Renal Impairment 15 mg pioglitazone /850 mg metformin hydrochloride (3)

Monitor patients for adverse events related to fluid retention after | Dosage Titration for Additional Glycemic Control

Specific Populations (8.6)].

(4), Warnings and Precautions (5.2)]

2.4 Recommendations for Congestive Heart Failure

45 mL/min, assess the benefit and risk of continuing therapy.

Monitoring for Fluid Retention and Dosage Modifications for Congestive Heart Failure

tablets debossed with "15/500" on one side and "1280" on other side.

Pioglitazone and metformin hydrochloride tablets are contraindicated in patients with

Severe renal impairment (eGFR below 30 mL/min) [see Warnings and Precautions (5.2)].

pioglitazone and metformin hydrochloride tablets and report these symptoms to their healthcare provide

ment of renal imp

events occur. discontinue pioglitazone and metformin hydrochloride tablets

pioglitazone controlled clinical trial database to date [see Adverse Reactions (6.1)].

patients without another explanation for the liver test abnormalities.

increased risk of bladder cancer associated with pioglitazone, while others did.

exposure to pioglitazone and bladder cancer [HR= 1.63; (95% CI: 1.22, 2.19)].

assessing and maintaining bone health according to current standards of care.

pioglitazone is a tumor promoter for urinary bladder tumors.

abnormal liver tests, pioglitazone and metformin hydrochloride should be initiated with caution.

of continuing therapy.

Radiological Studies with Contrast

Surgery and Other Procedu

Excessive Alcohol Intake

Hepatic Impairment

5.3 Edema

been received.

5.5 Hepatic Effects

5.6 Urinary Bladder Tumors

Cl: 0.89, 1.26)].

5.7 Fractures

5.8 Macular Edema

clinical or laboratory evidence of hepatic disease.

fluid intake.

Hypoxic States

Drug Interactions

<u>Age 65 or Greater</u> The risk of metforr

Populations (8.5)].

tablets debossed with "15/850" on one side and "1281" on other side.

below 30 mL/min.

Warning1.

tablets

- --- CONTRAINDICATIONS ----- In patients with established New York Heart Association (HA) Class III or IV heart failure at the time of pioglitazone and metformin hydrochloride tablets initiation [see Boxed Warning1, (4) In patients with severe renal impairment: (eGFR below 30 mL/
- min), (4) In patients with a history of serious hypersensitivity t pioglitazone, metformin HCI, or any of the excipients in pioglitazone and metformin hydrochloride tablets (4) In patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis. (4)
- ---- WARNINGS AND PRECAUTIONS ------Congestive heart failure: Fluid retention may occur and can exacerbate or lead to congestive heart failure. Combination use with insulin and use in congestive heart failure NYHA Class I and II may increase risk. Monitor patients for signs and symptoms. Edema: Dose-related edema may occur. (5.3)
- Hypoglycemia: Consider a lower dose of insulin or insulin secretagogue to reduce risk of hypoglycemia when used in combination with picture (152,000) (152,0 combination with pioglitazone and metformin hydrochloride tablets. (5.4)
- Hepatic effects: Postmarketing reports of hepatic failure, Clinical Pharmacology (12.3)]. is detected, promptly interrupt pioglitazone and metformin
- injury is confirmed and no alternate etiology can be found. (5.5) tablets if renal function is stable [see Warnings and Precautions (5.2)]. Urinary Bladder Tumors: May increase the risk of bladder 3 DOSAGE FORMS AND STRENGTHS cancer. Do not use in patients with active bladder cancer. Use aution when using in patients with a prior history of bladder cancer. (5.6)
- Fractures: Increased incidence in female patients. Apply 15 mg of pioglitazone and 850 mg of metformin HCI tablets, USP: white to off-white colored, capsule shaped, biconvex, film coated current standards of care for assessing and maintaining bone health. (5.7) Macular edema: Postmarketing reports. Recommend regular eye exams in all patients with diabetes according to current .
- standards of care with prompt evaluation for acute visual changes. (5.8) Vitamin B₁₂ deficiency: Metformin may lower vitamin B₁₂ levels. • A history of serious hypersensitivity to pioglitazone, metformin HCl, or any of the excipients in pioglitazone and metformin hydrochloride Nonitor hematologic parameters annually and vitamin $B_{\rm 12}$ at 2 to Acute or chronic metabolic acidosis, including diabetic ketoacidosis [see Warnings and Precautions (5.2)] 3 year intervals and manage any abnormalities. (5.9)
- 5 WARNINGS AND PRECAUTIONS
- ----- DRUG INTERACTIONS ------Pioglitazone and metformin hydrochloride tablets, are a combination of pioglitazone, a thiazolidinedione agonist of peroxisome indication of pioglitazone and metformin hydrochloride tablets dose to 15 mg/850 mg and metformin hydrochloride tablets dose to 15 mg/850 mg daily. (7.1) Lactic Acidosis There have been postmarketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were CYP2C8 inducers (e.g., rifampin) may decrease pioglitazone accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however
 - concentrations. (7.2)
 Carbonic anhydrase inhibitors may increase risk of lactic
 Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring. (7.3)
 brugs that reduce metformin clearance (such as ranolazine, uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk. vandetanib, dolutegravir, and cimetidine), may increase the If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along accumulation of metformin. Consider the benefits and risks of concomitant use. (7.4)
- Use of insulin secretagogues or insulin use may increase the risk Hemodialysis has often resulted in reversal of symptoms and recovery. for hypoglycemia and may require dose reduction. (7.6) Take or rally with meals to reduce gastrointestinal adverse Topiramate may decrease pioglitazone concentrations. (7.8) Topiramate may decrease pioglitazone concentrations. (7.8)
- pregnancy. (8.3) metformin 2 550 mp (2.2) Pediatrics: Safety and effectiveness have not been established. Pediatrics: Safety and effectiveness have not been established. Pediatrics: Safety and effectiveness have not been established. metformin 2,550 mg. (2.2) Recommended starting dosage in patients with NYHA Class I or Class II congestive heart failure is 15 mg of pioglitazone and 850 mn of metformin HCI orally once daily. (2.4) (8.4) Geriatric Use: Assess renal function more frequently. (8.5) Hepatic Impairment: Avoid use in patients with hepatic Hepatic Impairment: Avoid use in patients with hepatic
- - See 17 for PATIENT COUNSELING INFORMATION and Medication
- Before initiating pioglitazone and metformin hydrochloride tablets, obtain an eGFR. Revised: 3/2025
 - 7.5 Alcohol Insulin Secretagogues or Insul Drugs Affecting Glycemic Control
 - 8 USE IN SPECIFIC POPULATIONS
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 - 16 HOW SUPPLIED/STORAGE AND HANDLING 17 PATIENT COUNSELING INFORMATION
 - *Sections or subsections omitted from the full prescri
 - information are not listed.
- develops while taking pigilitazone and metformin hydrochloride tablets *[see Warnings* and *[see Warni*
- Steps to reduce the risk of and manage mettormin-associated lactic acidosis in these high-risk groups are provided in the Full Prescribing Information [see Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.2), Drug

Pioglitazone and Metformin Hydrochloride Tablets	COUNTRY : US	LOCATION : Inc	Irad		Supersedes A/W No.:	
Outsert	NO. OF COLORS: 1	REMARK :				V. No. : 01
Front Side	PANTONE SHADE NOS.:	SUBSTRATE : 4	0 g/m2 Bible Pap	er		
8099813	Black	Activities	Department	Name	Signature	Date
640 x 510		Prepared By	Pkg. Dev.			
S/S		Reviewed By	Pkg. Dev.			
07-03-2025	Font Size 6 pt_Med. 10 pt	Approved By	Quality			

Hospitalized, nonfatal

Note: Pharma code/ Bar code and adjacent text must be visible on folded leaflet These details can be moved by printed to arrange pharma code/ Bar code and adjacent text visible on folded leaflet. Patients with diabetes should have regular eye exams by an ophthalmologist according to current standards of care. Patients with diabetes **Table 8: Treatment-Emergent Adverse Events of Congestive Heart Failure (CHF) in Patients with NYHA Class II or III Congestive Heart** Titrate the pioglitazone and metformin hydrochloride tablets dosage gradually, as needed, after assessing therapeutic response and who report any visual symptoms should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or Hematologic Effects other physical findings [see Adverse Reactions (6.1)] In metrormin linical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12} -intrinsic factor complex, may 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. be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B₁₂ supplementation. Certain iduals (those with inadequate vitamin B₁₂ or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B₁₂ Creatine Phosphokinase levels. Measure hematologic parameters on an annual basis and vitamin B₁₂ at 2 to 3 year intervals in patients on pioglitazone and metformin

ochloride and manage any abnormalities [see Adverse Reactions (6.1)]. The following serious adverse reactions are discussed elsewhere in the labeling Congestive heart failure [see Boxed Warning, Warnings and Precautions (5.1)]

Lactic acidosis [see Boxed Warning, Warnings and Precautions (5.2)] Edema [see Warnings and Precautions (5.3)]

Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues [see Warnings and Precautions (5.4)] Hepatic Effects [see Warnings and Precautions (5.5)] Irinary Bladder Tumors [see Warnings and Precautions (5.6)]

Macular Edema [see Warnings and Precautions (5.8] Vitamin B_{12} Levels [see Warnings and Precautions (5.9]

cause clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot After initiation of pioglitazone and metformin hydrochloride tablets or with dosage increase, monitor patients carefully for adverse reactions be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

If congestive heart failure develops while taking pioglitazone and metformin hydrochloride tablets, consider discontinuation of pioglitazone of ver 8,500 patients with type 2 diabetes mellitus have been treated with pioglitazone in randomized, double-blind, controlled clinical trials, and metformin hydrochloride tablets or dosage reduction of pioglitazone in pioglitazone and metformin hydrochloride tablets *(see Boxed)* including 2,605 patients with type 2 diabetes mellitus and macrovascular disease treated with pioglitazone from the PROactive clinical trial In these trials, over 6,000 patients have been treated with pioglitazone for six months or longer, over 4,500 patients have been treated with pioglitazone for one year or longer, and over 3,000 patients have been treated with pioglitazone for at least two years. The maximum recommended dosage of pioglitazone and metformin hydrochloride tablet is one tablet (15 mg of pioglitazone and 850 mg In six pooled 16 to 26 week placebo-controlled monotherapy and 16 to 24 week add-on combination therapy trials. the incidence of

of metformin HCI) once daily when used in combination with gemfibrozil or other strong CYP2C8 inhibitors [see Drug Interactions (7.1), withdrawals due to adverse events was 4.5% for patients treated with pioglitazone and 5.8% for comparator-treated patients. The most (1.5%) with pioglitazone than with placebo (3.0%).

Common Adverse Events: 16 to 26 Week Monotherapy Trials

DOSAGE FORMS AND STRENGTHS 15 mg of pioglitazone and 500 mg of metformin HCI tablets, USP: white to off-white colored, capsule shaped, biconvex, film coated in patients treated with pioglitazone than in patients who received placebo. None of these adverse events were related to the pioglitazone

Table 2: 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 Pionlitazone than in Patients Treated with Placeho % of Patients

76 011 410110				
	Placebo N=259	Pioglitazone N=606		
Tract Infection	8.5	13.2		
	6.9	9.1		
	4.6	6.3		
	2.7	5.4		
	0.8	5.1		

Common Adverse Events: 16 to 24 Week Add-on Combination Therapy Trials A summary of the overall incidence and types of common adverse events reported in trials of pioglitazone add-on to metformin is provided CABG = coronary artery bypass grafting; PCI = percutaneous intervention reduction of pioglitazone and metformin hydrochloride [see Boxed Warning, Contraindications (4), Adverse Reactions (6.1)]. in Table 3. Terms that are reported represent those that occurred at an incidence of >5% and more commonly with the highest tested dose Weight Gain

	16 Week Placebo- Adverse Events Reported in >5% of Pati Treated with Pioglita than in Patients Treated wi	ents and More Commonly in Patients zone + Metformin			
	% of Pat	% of Patients			
	Placebo +Metformin N=160	Pioglitazone 30 mg + Metformin N=168			
Edema	2.5	6.0			
Headache	1.9	6.0			
	24 Week Non-Controlled Double-Blind Trial Advers Commonly in Patients Treated with Pioglitazone 4 Pioglitazone 30 m	5 mg + Metformin than in Patients Treated with			
	% of Patients				
	Pioglitazone 30 mg +Metformin N=411	Pioglitazone 45 mg + Metformin N=416			
	10.4	13.5			
Upper Respiratory Tract Infection	12.4	13.0			
	5.8	13.9			
Tract Infection					

rms of edema peripheral, generalized edema, pitting edema, and Common Adverse Events: 24 Week Pioplitazone and Metformin Hydrochloride Tablets Clinical Trial

and metformin hydrochloride tablets dosed twice daily in patients with inadequate glycemic control on diet and exercise (N=600). Table 4: Adverse Events (≥5% for Pioglitazone and Metformin Hydrochloride Tablets) Reported by Patients with Inadequate Glycen Control on Diet and Exercise in a 24 Week Double-Blind Clinical Trial of Pioglitazone and Metformin Hydrochloride Tablet:

	% of Patients					
	Pioglitazone and Metformin Hydrochloride Tablets 15/850 mg Twice Daily N=201	Pioglitazone 15 mg Twice Daily N=190	Metformin 850 mg Twice Daily N=209	-		
	9.0	2.6	15.3			
	5.5	2.6	4.8			
I,	abdominal pain was reported in 2.0% of	patients in the pioglitazone and metfo	rmin hydrochloride group, 1.6% in th	6		

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

(particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, Table 5: PROactive Trial: Incidence and Types of Adverse Events Reported in >5% of Patients Treated with Pioglitazone and More Commonly than Placebo

% of Patients

26.7

8.1

64

Placebo N=2,633 Pioglitazone N=2,605 27.3 18.8 15.3

should be used with caution in patients at risk for congestive heart failure. Patients treated with pioglitazone and metformin hydrocholoride A summary of the incidence of adverse events related to congestive heart failure is provided in Table 6 for the 16 to 24 week add-on to

rmin trials. None of the events were fata Table 6: Treatment-Emergent Adverse Events of Congestive Heart Failure (CHF) Patients Treated with Pioglitazone or Placebo Added on

in					
Number (%) of Patients					
	Placebo-Controlled Trial (16 weeks)		Double-	Blind Trial	
	Placebo + Metformin N=160	Pioglitazone 30 mg + Metformin N=168	Pioglitazone 30 mg +Metformin N=411	Pioglitazone 45 mg + Metformin N=416	
tive	0	1 (0.6%)	0	1 (0.2%)	
	0	1 (0.6%)	0	1 (0.2%)	
Emerg	gent Adverse Events of Cong	Non-Controlled Trial (16 weeks) Piacebo-Controlled Trial (24 weeks) Bind Trial (24 weeks) Sebo formin 160 Pioglitazone 30 mg + Metformin N=168 Pioglitazone 30 mg + Metformin N=411 Pioglitazone 45 mg + Metformin N=416 O 1 (0.6%)			
th Pio	glitazone or Placebo Added	on to a Sulfonylurea			
		Number (%) o	f Patients		

	Placebo-Controlled Trial (16 weeks)			Non-Controlled Double-Blind Trial (24 weeks)	
	Placebo + Sulfonylurea N=187	Pioglitazone 15 mg + Sulfonylurea N=184	Pioglitazone 30 mg + Sulfonylurea N=189	Pioglitazone 30 mg + Sulfonylurea N=351	Pioglitazone 45 mg + Sulfonylurea N=351
At least one con- gestive heart failure event	2 (1.1%)	0	0	1 (0.3%)	6 (1.7%)
Hospitalized	2 (1.1%)	0	0	0	2 (0.6%)
Patients Treated with Pioglitazone or Placebo Added on to Insulin					

	· · · · · · · · · · · · · · · · · · ·						
	Number (%) of Patients						
	P	lacebo-Controlled Tria (16 weeks)	Non-Controlled Double-Blind Trial (24 weeks)				
	Placebo + Insulin N=187	Pioglitazone 15 mg + Insulin N=191	Pioglitazone 30 mg + Insulin N=188	Pioglitazone 30 mg + Insulin N=345	Pioglitazone 45 mg + Insulin N=345		
	0	2 (1.0%)	2 (1.1%)	3 (0.9%)	5 (1.4%)		
	0	2 (1.0%)	1 (0.5%)	1 (0.3%)	3 (0.9%)		
th Pioglitazone or Placebo Added on to Metformin			-				
Number (%) of Patients							
	Placebo-Controlled Tri (16 weeks)		l		ouble-Blind Trial eeks)		
	Placebo + Metformin N=160		oglitazone 30 mg Vetformin N=168	Pioglitazone 30 mg + Metformin N=411	Pioglitazone 45 mg + Metformin N=416		

1 (0.6%)

1 (0.6%

Failure Treated with Pioglitazone or Glyburide			
	Number (%)	of Subjects	
	Pioglitazone N=262	Glyburide N=256	
Death due to cardiovascular causes (adjudicated)	5 (1.9%)	6 (2.3%)	
Overnight hospitalization for worsening CHF (adjudicated)	26 (9.9%)	12 (4.7%)	
Emergency room visit for CHF (adjudicated)	4 (1.5%)	3 (1.2%)	
Patients experiencing CHF progression during study	35 (13.4%)	21 (8.2%)	
ngestive heart failure events leading to hospitalization that occ	urred during the PROactive trial are si	ummarized in Table 9.	
ole 9: Treatment-Emergent Adverse Events of Congestive Hea	art Failure (CHF) in PROactive Trial		
	Number (%)	of Patients	
	Placebo N=2,633	Pioglitazone N=2,605	
At least one hospitalized congestive heart failure event	108 (4.1%)	149 (5.7%)	
Fatal	22 (0.8%)	25 (1.0%)	

rdiovascular Safet In the PROactive trial, 5,238 patients with type 2 diabetes mellitus and a history of macrovascular disease were randomized to pioolitazone (H=2,605), force-titrated up to 45 mg daily or placebol (N=2,605) 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, pirin, 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 Eye Disorders: New onset or worsening diabetic macular edema with decreased visual acuity 8.1%. Mean duration of follow-up was 34.5 months.

86 (3.3%)

124 (4.7%)

The primary objective of this trial was to examine the effect of pioglitazone on mortality and macrovascular morbidity in patients with type 2 diabetes mellitus who were at high risk for macrovascular events. The primary efficacy variable was the time to the first occurrence of any event in a cardiovascular composite endpoint that included all-cause mortality, nonfatal myocardial infaction (MI) including silent MI, stroke, acute coronary syndrome, cardiac intervention including coronary artery bypass grafting or percutaneous intervention, major leg amputation above the ankle, and bypass surgery or revascularization in the leg. A total of 514 (19.7%) patients treated with pioplitazone and common adverse events leading to withdrawal were related to inadequate glycemic control, although the incidence of these events was lower 572 (21.7%) placebo-treated patients experienced at least one event from the primary composite endpoint (HR = 0.90; 95% CI: 0.80, 1.02; p=0.10)

In the PROactive trial, the incidence of withdrawals due to adverse events was 9.0% for patients treated with pioglitazone and metformin hydrochloride tablets at the incidence of a first event within placebo for the three year incidence of a first event within placebo for the three year incidence of a first event within placebo for the three year incidence of a first event within placebo for the three year incidence of a first event within placebo for the three year incidence of a first event within placebo for the three year incidence of a first event within placebo for the three year incidence of a first event within placebo for the three year incidence of a first event within placebo for the three year incidence of a first event within placebo-treated patients. Congestive heart failure; or in patients with a history of liver disease, alcoholism, or heart failure; or in patients with a history of placebo for the three year incidence of a first event within placebo-treated patients. Congestive heart failure; or in patients treated with placebo. Table 10: PROactive Trial: Number of First and Total Events for Each Component Within the Cardiovascular Composite Endpoint

	Placebo N=2.633		Pioglitazone N=2.605	
Cardiovascular Events	First Events n (%)	Total events n	First Events n (%)	Total events n
Any event	572 (21.7)	900	514 (19.7)	803
All-cause mortality	122 (4.6)	186	110 (4.2)	177
Nonfatal myocardial infarction (MI)	118 (4.5)	157	105 (4.0)	131
Stroke	96 (3.6)	119	76 (2.9)	92
Acute coronary syndrome	63 (2.4)	78	42 (1.6)	65
Cardiac intervention (CABG/PCI)	101 (3.8)	240	101 (3.9)	195
Major leg amputation	15 (0.6)	28	9 (0.3)	28
Leg revascularization	57 (2.2)	92	71 (2.7)	115

Dose-related weight gain occurs when pioglitazone is used alone or in combination with other antidiabetic medications. The mechanism of

weight gain is unclear but probably involves a combination of fluid retention and fat accumulation. Tables 11, 12, and 13 summarize the changes in body weight with pioglitazone and placebo in the 16 to 26 week randomized, doubleblind monotherapy and 16 to 24 week combination add-on therapy trials, the PROactive trial, and the 24 week pioglitazone and metformin hydrochloride trial Table 11: Weight Changes (kg) from Possiins During Dandomized, Double Blind Official Table

ladie III: weight Changes (kg) from Baseline During Randomized, Double-Blind Clinical Irlais							
		Control Group (Placebo)	Pioglitazone 15 mg	Pioglitazone 30 mg	Pioglitazone 45 mg		
		Median Median (25 th , 75 th (25 th , 75 th) percentile) percentile)		Median (25ʰ, 75ʰ percentile)	Median (25 th , 75 th percentile)		
Monotherapy (16 to 26 weeks)		-1.4 (-2.7, 0.0) N=256	0.9 (-0.5, 3.4) N=79	1.0 (-0.9, 3.4) N=188	2.6 (0.2, 5.4) N=79		
Combination	Sulfonylurea	-0.5 (-1.8, 0.7) N=187	2.0 (0.2, 3.2) N=183	3.1 (1.1, 5.4) N=528	4.1 (1.8, 7.3) N=333		
Therapy (16 to 24 weeks)	Metformin	-1.4 (-3.2, 0.3) N=160	N/A	0.9 (-1.3, 3.2) N=567	1.8 (-0.9, 5.0) N=407		
	Insulin	0.2 (-1.4, 1.4) N=182	2.3 (0.5, 4.3) N=190	3.3 (0.9, 6.3) N=522	4.1 (1.4, 6.8) N=338		

Table 12: Median Change in Body Weight in Patients Treated with Pioglitazone vs Patients Treated with Placebo During the Double-Blind Treatment Period in the PROactive Tria

	Placebo	Pioglitazone
	Median (25 th , 75 th percentile)	Median (25 ^m , 75 ^m percentile)
Change from baseline to final visit (kg)	-0.5 (-3.3, 2.0) N=2,581	+3.6 (0.0, 7.5) N=2,560
dian exposure for both pipelitazone and placet	was 2.7 years	

ote: Median exposure for both pioglitazone and placebo was 2.7 years The concomitant use of pioglitazone and metformin hydrochloride with specific drugs may increase the risk of metformin-associated lactic Table 4 summarizes the incidence and types control on dist and avarrise (N=600)

in Patients with Inadequate Glycer	mic Control on Diet and Exercise	;	
	Pioglitazone and Metformin Hydrochloride Tablets 15/850 mg Twice Daily	Pioglitazone 15 mg Twice Daily	Metformin 850 mg Twice Daily
	Median (25 th , 75 th percentile)	Median (25 th , 75 th percentile)	Median (25 th , 75 th percentile)
Change from baseline to final visit (kg)	1.00 (-1.0, 3.0)	1.35 (-0.7, 4.1)	-1.00 (-2.6, 0.4)

Note: Trial duration of 24 wee Edema induced from taking pioglitazone is reversible when pioglitazone is discontinued. The edema usually does not require hospitalization by body surface area. unless there is co-existing congestive 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 HCI did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits up to 600 mg/ 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 14. Table 14: Adverse Events of Edema in Patients Treated with Pioglitazone

Number (%) of Patients Pioglitazone Pioglitazone Pioglitazone Placebo 15 mg 30 mg 45 mg 3 (1.2%) N=259 2 (2.5%) 13 (4.7%) 11 (6.5%) (16 to 26 week N= 81 N= 275 N=169

4 (2.1%) 3 (1.6%) 61 (11.3%) N=540 81 (23.1%) N=351 Sulfonvlure N=187 N=184 ined Therapy 4 (2.5%) N/A 34 (5.9%) N=579 58 (13.9%) N=416 /letformin (16 to 24 weeks N=160 13 (7.0%) N=187 24 (12.6%) 109 (20.5%) N=533 90 (26.1%) N=345 N=191

Note: The preferred terms of edema peripheral, gen eralized edema, pitting edema, and fluid retention were combined to form the aggregate term of "edema.

term of "edema.

Number (%) of Patients					
Placebo N=2,633	Pioglitazone N=2,605				
419 (15.9%)	712 (27.3%)				
te: The preferred terms of edema peripheral, generalized edema, pit	tting edema, and fluid retention were combined to form the aggregate				

Hepatic Effects There has been no evidence of pioglitazone einduced hepatotoxicity in the pioglitazone controlled clinical trial database to date. One randomized, double-blind, three year trial comparing pioglitazone to glyburide as add-on to metformin and insulin therapy was specifically $\frac{1}{100} \frac{1}{100} \frac{1}$ 9/1,046 (0.9%) patients treated with glyburide developed ALT values greater than three times the upper limit of the reference range. None of the patients treated with pioglitazone in the pioglitazone controlled clinical trial database to date have had a serum ALT greater than three times the upper limit of the reference range and a corresponding total bilirubin greater than two times the upper limit of the reference range. a combination predictive of the potential for severe drug-induced liver injury

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

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 ulfonylurea trial (15.7% vs 13.4%) and in the 24-week add-on to insulin trial (47.8% vs 43.5%).

Three patients in these four trials were hospitalized due to hypoglycemia. All three patients were receiving pioglitazone 30 mg (0.9%) in 8.6 Renal Impairment 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 the degree of the patient's usual activities in the patient's usual activities in the degree of the patient's usual activities in the degree of the patient's usual activities in the patient's usual activities in the degree of the patient's usual activities in the degree of the patient's usual activities in the patient's usual activities and metric activities and metri sulfonylurea (n=2) or pioglitazone 30 mg or 45 mg in combination with insulin (n=12). Urinary Bladder Tumors

Tumors were observed in the urinary bladder of male rats in the two year carcinogenicity study *[see Nonclinical Toxicology (13.1)]*. During the three-year PROactive clinical trial, 14 patients out of 2,605 (0.54%) randomized to pioglitazone and 5 out of 2,633 (0.19%) randomized to pioglitazone and metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Pioglitazone and metformin to placebo were diagnosed with bladder cancer. After excluding patients in whom exposure to study drug was less than one year at the time hydrochloride tablets are not recommended in patients with hepatic impairment [see Warnings and Precautions (5.2)]. a large subset of patients was observed for up to 10 additional years, with little additional exposure to pioglitazone. During the 13 years of both PROactive and observational follow-up, the occurrence of bladder cancer did not differ between patients randomized to pioglitazone or placebo (HR = 1.00; [95% CI: 0.59 1.72]) [see Warnings and Precautions (5.6)].

Metformin HCI In a double-blind clinical study of metformin in patients with type 2 diabetes mellitus, a total of 141 patients received metformin therapy (up to 2,550 mg per day) and 145 patients received placebo. Adverse reactions reported in greater than 5% of the metformin patients, and that were more common in metformin than placebo-treated patients, are listed in Table 16. In this trial, diarrhea led to discontinuation of study medication in 6% of patients treated with metformin.

	Metformin Monotherapy (n=141)	Placebo (n=145)	
Adverse Reaction	% of Pat	ents	
Diarrhea	53.2	11.7	
Nausea/Vomiting	25.5	8.3	
Flatulence	12.1	5.5	
Asthenia	9.2	5.5	
Indigestion	7.1	4.1	
Abdominal Discomfort	6.4	4.8	

mon in metformin than placebo-treated patient * Reactions that were more co

jolitazone may cause decreases in hemoglobin and hematocrit. In placebo-controlled monotherapy trials, mean hemoglobin value: declined by 2% to 4% in patients treated with pioglitazone compared with a mean change in hemoglobin of -1% to +1% in placebo-treated patients. These changes primarily occurred within the first four to 12 weeks of therapy and remained relatively constant thereafter. These

During protocol-specified measurement of serum creatine phosphokinase (CPK) in pioglitazone clinical trials, an isolated elevation in CPK to greater than 10 times the upper limit of the reference range was noted in nine (0.2%) patients treated with pioglitazone (values of 2,150 to 11,400 IU/L) and in no comparator- treated patients. Six of these nine patients continued to receive pioglitazone, two patients were noted to have the CPK elevation on the last day of dosing, and one patient discontinued pioglitazone due to the elevation. These elevations resolved without any apparent clinical sequelae. The relationship of these events to pioglitazone therapy is unknown.

Vitamin B12 Concentrations In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B₁₂ levels was observed

in approximately 7% of patients. 6.2 Postmarketing Experience The following adverse reactions have been identified during post-approval use of pioglitazone and/or metformin. Because these reactions

are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure Cardiac Disorders: Rapid increases in weight, edema, congestive heart failure with and without previously known heart disease or

concomitant insulin administration Hepatobiliary Disorders: Fatal and nonfatal hepatic failure

Metformin Hepatobiliary Disorders: Cholestatic, hepatocellular, and mixed hepatocellular liver injury

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_{12}) of pioglitazone. Therefore, the maximum recommended dosage of pioglitazone and metformin hydrochloride tablets is 15 mg of pioglitazone and 850 mg of metformin HCl once daily if used in combination with gemfibrozil or other strong CYP2C8 inhibitors [see Dosage and Administration (2.3), 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 and metformin hydrochloride tablets, changes in diabetes treatment may be needed based on clinical response without exceeding the maximum recommended daily dosage of pioglitazone and metformin hydrochloride tablets (45 mg of pioglitazone and 2,550 mg of metformin HCI) [see Clinical Pharmacology (12.3)]. 7.3 Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with pioglitazone and metformin hydrochloride 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.a..

organic cationic transporter-2 [OCT2]/multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis [see Clinical Pharmacology (12.3)]. Consider the benefits and risks of concomitant use. 7.5 Alcohol Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving

pioglitazone and metformin hydrochloride tablets. 7.6 Insulin Secretagogues or Insulin Coadministration of pioglitazone and metformin hydrochloride with an insulin secretagogue (e.g., sulfonylurea) or insulin may increase

the risk of hypoglycemia. If hypoglycemia occurs in a patient coadministered pigglitazone and metformin hydrochloride and an insulin secretagogue (e.g., sulfonylurea), the dose of the insulin secretagogue should be reduced. 7.7 Drugs Affecting Glycemic Control Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium

channel blockers, and isoniazid. When such drugs are administered to a patient receiving pioglitazone and metformin hydrochloride tablets, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving pioglitazone and metformin hydrochloride tablets, the patient should be observed closely for hypoglycemia. 7.8 Topiramate

A decrease in the exposure of pioglitazone and its active metabolites were noted with concomitant administration of pioglitazone and topiramate [see Clinical Pharmacology (12.3)]. The clinical relevance of this decrease is unknown; however, when pioglitazone and metformin hydrochloride and topiramate are used concomitantly, monitor patients for adequate glycemic control. 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Risk Summary

Limited data with pipolitazone and metformin hydrochloride or pipolitazone in pregnant women are not sufficient to determine a drugassociated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a clear associated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk (see Data). There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [see Clinical Considerations]. In animal reproduction studies, no adverse developmental effects were observed when pioglitazone was administered to pregnant rats and rabbits during organogenesis at exposures up to 5 and 35 times the 45 mg clinical dose, respectively, based on body surface area. No adverse

developmental effects were observed when metformin was administered to prepare the part of and a trabits during the period of organogenesis at doses up to 2 to 6 times, respectively, a 2,000 mg clinical dose, based on body surface area (see Data). The estimated background risk of major birth defects is 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 for the indicated population is unknown. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations Disease-Associated Maternal and/or Embrvo/Fetal Risk Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, still birth and delivery of notications. Poorly controlled diabetes increases the fetal risk for major birth defects still birth and macrosomia related morbidity

Data Human Data

Published data from postmarketing 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 comparato

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

kg/day during the period of organogenesis. This represents an exposure of about 2 to 6 times a 2,000 mg clinical dose based on body surface area (mg/m²) for rats and rabbits, respectively. 8.2 Lactation

Risk Summary There is no information regarding the presence of pioglitazone and metformin hydrochloride or pioglitazone in human milk, the effects on the breastied infant, or the effects on milk production. Pioglitazone is present in rat milk; however, due to species-specific differences in latation 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 breastfeed infant and no available information on the effects of metformin on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for pioplitazone and metformin hydrochloride tablets and any potential adverse effects on the breastfed

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

8.3 Females and Males of Reproductive Potential Discuss the potential for unintended pregnancy with premenopausal women as therapy with pioglitazone and metformin hydrochloride tablets, may result in ovulation in some anovulatory women

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

8.5 Geriatric Use

Pioglitazone A total of 92 patients (15.2%) treated with pioglitazone in the three pooled 16 to 26 week double-blind, placebo-controlled, monotherapy trials were \geq 65 years old and two patients (0.3%) were \geq 75 years old. In the two pooled 16 to 24 week add-on to sulforylurea trials, 201

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 \geq 75 years old.

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently In the 16 week add-on to sulfonylurea trial, the incidence of reported hypoglycemia was 3.7% with pioglitazone 30 mg and 0.5% with pioglitazone 15 mg, 15.4% with pioglitazone 16 mg and 0.5% with pioglitazone 16 mg and 0.5% with pioglitazone 16 mg and 0.5% with pioglitazone 17 mg and 0.5% with pioglitazone 16 mg and 0.5% with pioglitaz 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), Dosage and Admin (2.2)].

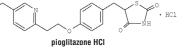
> Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of with an eGFR below 30 mL/min [see Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.2), Clinical Pharmacology (12.3)].

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

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

overdosage is suspected In the event of overdosage. contact the Poison Help Line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations. Appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. 11 DESCRIPTION Pioglitazone and metformin hydrochloride tablets, USP are a thiazolidinediones and biguanide combination product that contains two oral

antidiabetic medications: pioglitazone HCI and metformin HCI. Pioglitazone [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy]phenyl]methyl]-2.4-] thiazolidinedione monohydrochloride contains one asymmetric carbon, and the compound is synthesized and used as the racemic mixture. The two enantiomers of pioglitazone interconvert in vivo. No differences were found in the pharmacologic activity between the two enantiomers. The structural formula is as shown:



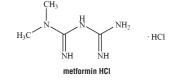
Laboratory Abnormalities

1 (0.2%)

1 (0.2%)

Note: Pharma code/ B				
DATE	:			
ART WORK SIZE	:			
DIMENSIONS (MM)	:			
CODE	:			
DESIGN STYLE	:			
ITEM / PACK	:			
PRODUCT NAME	:			

Pioglitazone HCI, USP is an odorless white crystalline powder that has a molecular formula of C10HanNaO35+HCI and a molecular weight Patients with Renal Impairmen of 392.90 dattors. It is soluble in *N*.*N*-dimethylformamide, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water, and insoluble in ether. and a molecular weight of 165.62. Metformin HCl is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin HCl is 6.68. The structural formula is as shown: Metformin HCl is $\frac{1}{1000}$ Metformin HCI (N.N-dimethylimidodicarbonimidic diamide HCI), USP is a white crystalline powder with a molecular formula of C₄H₁₁N₄+HCI



ioglitazone and metformin hydrochloride tablets, USP are available as a tablet for oral administration containing 15 mg pioglitazone (as the base) with 500 mg metformin hydrochloride (15 mg/500 mg) or 15 mg pioglitazone (as the base) with 850 mg metformin hydrochloride (15 mg/850 mg) formulated with the following excipients: croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, and titanium dioxide. 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action Pioglitazone and metformin hydrochloride tablets combine two antihyperglycemic agents: pioglitazone and metformin

Pioglitazone is a thiazolidinedione that depends on the presence of insulin for its mechanism of action. Pioglitazone decreases insulin Table 18: Effect of Pioglitazone Coadministration on Systemic Exposure of Other Drugs resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output oglitazone is not an insulin secretagogue. Pioglitazone is an agonist for peroxisome proliferator-activated receptor-gamma (PPAR_Y). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARy nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism. In animal models of diabetes, pioglitazone reduces the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulinresistant states such as type 2 diabetes mellitus. The metabolic changes produced by pioglitazone result in increased responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance Because pioglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal

models that lack endogenous insulin.

Metformin HCl improves olucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not produce hypoglycemia in either patients with type 2 diabetes mellitus or healthy subjects [except in specific circumstances, see Warnings and Precautions (5.4)] and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease. 12.2 Pharmacodynamics

<u>Pioglitazone</u> Clinical studies demonstrate that pioglitazone improves insulin sensitivity in insulin-resistant patients. Pioglitazone enhances cellula responsiveness to insulin, increases insulin-dependent glucose disposal and improves hepatic sensitivity to insulin. In patients with type 2 iabetes mellitus, the decreased insulin resistance produced by pioglitazone results in lower plasma glucose concentrations, lower plasma insulin concentrations, and lower HbA1c values. In controlled clinical trials, pioglitazone had an additive effect on glycemic control when used in combination with a sulfonylurea, metformin, or insulin [see Clinical Studies (14)] Patients with lipid abnormalities were included in clinical trials with pioglitazone. Overall, patients treated with pioglitazone had mean

decreases in serum triglycerides, mean increases in HDL cholesterol, and no consistent mean changes in LDL and total cholesterol. There is o conclusive evidence of macrovascular benefit with pioglitazone [see Adverse Reactions (6.1)]. In a 26 week, placebo-controlled, dose-ranging monotherapy study, mean serum triglycerides decreased in the 15 mg, 30 mg, and 45 mg pioglitazone dose groups compared to a mean increase in the placebo group. Mean HDL cholesterol increased to a greater extent in natient ed with pioglitazone than in the placebo-treated patients. There were no consistent differences for LDL and total cholesterol in patients treated with pioglitazone compared to placebo (see Table 17).

	Placebo	Pioglitazone 15 mg Once Daily	Pioglitazone 30 mg Once Daily	Pioglitazone 45 mg Once Daily
Triglycerides (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	263	284	261	260
Percent change from baseline (adjusted mean*)	4.8%	-9.0%†	-9.6%†	-9.3%†
HDL Cholesterol (mg/dL)	N=79	N=79	N=83	N=77
Baseline (mean)	42	40	41	41
Percent change from baseline (adjusted mean*)	8.1%	14.1%†	12.2%	19.1%†
LDL Cholesterol (mg/dL)	N=65	N=63	N=74	N=62
Baseline (mean)	139	132	136	127
Percent change from baseline (adjusted mean*)	4.8%	7.2%	5.2%	6.0%
Total Cholesterol (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	225	220	223	214
Percent change from baseline (adjusted mean*)	4.4%	4.6%	3.3%	6.4%

In the two other monotherapy studies (16 weeks and 24 weeks) and in combination therapy studies with metformin (16 weeks and 24 weeks), the results were generally consistent with the data above.

† p <0.05 vs placebo</p>

Absorption Pioglitazone and metformin hydrochloride tablets In bioequivalence studies of pioglitazone and metformin hydrochloride tablets 15 mg/500 mg and 15 mg/850 mg, the area under the

curve (AUC) and maximum concentration (C____) of both the pionitazone and the metformin component following a single dose of the ation tablet were bioequivalent to ACTOS 15 mg concomitantly administered with metformin HCl immediate release (500 mg or 850 mg, respectively) tablets under fasted conditions in healthy subjects.

Administration of pioglitazone and metformin hydrochloride tablets 15 mg/850 mg with food resulted in no change in overall exposure of pioglitazone. With metformin there was no change in AUC; however, mean peak serum concentration of metformin was decreased by 28% when administered with food. A delayed time to peak serum concentration was observed for both components (1.9 hours for pioglitazone and 0.8 hours for metformin) under fed conditions. These changes are not likely to be clinically significant

Following once-daily administration of pionlitazone, steady-state serum concentrations of both pionlitazone and its major active metabolite M-III (keto derivative of pioglitazone) and M-IV (hydroxyl derivative of pioglitazone), are achieved within seven days. At steady state M-III and M-IV reach serum concentrations equal to or greater than that of pioglitazone. At steady state, in both healthy volunteers and patients with type 2 diabetes mellitus, pioglitazone comprises approximately 30 to 50% of the peak total pioglitazone serum concentrations (pioglitazone plus active metabolites) and 20 to 25% of the total AUC.

Cmax, AUC, and trough serum concentrations (Cmin) for pioglitazone and M-III and M-IV, increased proportionally with administered doses o 15 mg and 30 mg per day. Following oral administration of pioglitazone, T_{max} of pioglitazone was within two hours. Food delays the T_{max} to three to four hours, but does not alter the extent of absorption (AUC).

Metformin HCI of metformin, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 mcg/mL. During Additional decrease in active metabolites; 60% for M-III and 16% for M-IV.

controlled clinical trials, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses. Food decreases the rate and extent of metformin absorption, as shown by a 40% lower mean C_{max}, a 25% lower AUC, and a 35 minute Table 20: Effect of Coadministered Drug on Plasma Metformin Systemic Exposu prolongation of T_{max} following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown. Distribution

The mean apparent volume of distribution (Vd/F) of pioglitazone following single-dose administration is 0.63 ± 0.41 (mean ± SD) L/kg of bod weight. Pioglitazone is extensively protein bound (>99%) in human serum, principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. M-III and M-IV are also extensively bound (>98%) to serum albumin.

Metformin HCI The Vd/F of metformin following single oral doses of 850 mg immediate-release metformin averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time Elimination

Pioglitazone

Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-III and M-IV are the major circulating active metabolites in humans. In vitro data demonstrate that multiple CYP isoforms are involved in the metabolism of pioplitazone which include CYP2C8 and, to a lesser degree, CYP3A4 with additional contributions from a variety of other isoforms, including the mainly extrahepatic CYP1A1. In vivo study of pioglitazone in combination with gemfibrozil, a strong CYP2C8 inhibitor, showed that pioglitazone is a CYP2C8 substrate [see Dosage and Administration (2.3), Drug Interactions (7.1)]. Urinary 6B-hydroxycortisol/cortisol ratios measured in patients treated with pioglitazone showed that pioglitazone is not a strong CYP3A4 enzyme inducer.

Metformin HCI ntravenous single-dose studies in healthy subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo *All metformin and coadministered drugs were given as single doses. hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Pioglitazone Following oral administration, approximately 15 to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone AUC = AUC use 12h Following oral administration, approximately to to 30% of the programme use is recovered in the time, note dimensional or programme and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into **Table 21: Effect of Metformin on Coadministered Drug Systemic Exposure** the bile either unchanged or as metabolites and eliminated in the feces. The mean serum half-life ($t_{\rm rz}$) of pioglitazone and its metabolites (M-III and M-IV) range from three to seven hours and 16 to 24 hours,

respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be five to seven L/hi Metformin HCI Renal clearance is approximately 3.5 times greater than creatinine clearance (CrCl), which indicates that tubular secretion is the maio route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal

route within the first 24 hours, with a plasma elimination $t_{1/2}$ of approximately 6.2 hours. In blood, the elimination $t_{1/2}$ is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution Specific Populations Geriatric Patients

<u>Pioglitazone</u>

In healthy elderly subjects, C_{max} of pioglitazone was not significantly different, but AUC values were approximately 21% higher than those achieved in younger subjects. The mean t_{s} of pioglitazone was also prolonged in elderly subjects (about ten hours) as compared to younger subjects (about seven hours). These changes are not considered clinically relevant. Metformin HCI imited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total CL/F is decreased, the t_{ki} is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin

pharmacokinetics with aging is primarily accounted for by a change in renal function. Pediatric Patients Pioalitazone Safety and efficacy of pioglitazone in pediatric patients have not been established. Pioglitazone and metformin hydrochloride is not

recommended for use in pediatric patients [see Use in Specific Populations (8.4)]. After administration of a single oral metformin 500 mg tablet with food, geometric mean metformin C_{max} and AUC differed less than 5%

between pediatric type 2 diabetic patients (12 to 16 years of age) and gender- and weight-matched healthy adults (20 to 45 years of age), and all with normal renal function Male and Female Patients Pioglitazone The mean C_{max} and AUC values of pioglitazone were increased 20 to 60% in females compared to males. In controlled clinical trials, HbA1c

be individualized for each patient to achieve glycemic control, no dosage adjustment is recommended based on gender alone Metformin HCI

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender (males=19, females=16). Similarly, in controlled clinical studies in patients with type 2 diabetes mellitus, the cause of the hyperplastic changes antihyperglycemic effect of metformin was comparable in males and females. Racial or Ethnic Groups

<u>Pioglitazone</u> Pharmacokinetic data among various ethnic groups are not available

Metformin HCI No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes mellitus, the antihyperglycemic effect was comparable in Whites (n=249), Blacks or African Americans (n=51), and an *in vivo* micronucleus assay. and Hispanics or Latinos (n=24).

severe (CrCl <30 mL/min) renal impairment when compared to subjects with normal renal function. Therefore, no dosage adjustment in

Dosage and Administration (2.3), Contraindications (4), Warnings and Precautions (5.2)]. Patients with Hepatic Impairment Compared with healthy controls, subjects with impaired hepatic function (Child-Turcotte-Pugh Grade B/C) have an approximate 45% negative.

eduction in pioglitazone and total pioglitazone (pioglitazone, M-III, and M-IV) mean C_{max} but no change in the mean AUC values. Therefore, no dosage adjustment in patients with hepatic impairment is required. There are postmarketing reports of liver failure with pioglitazone and clinical trials have generally excluded patients with serum ALT >2.5 based on body surface area comparisons. imes the upper limit of the reference range. Use pioglitazone and metformin hydrochloride tablets with caution in patients with liver disease 13.2 Animal Toxicology and/or Pharmacology [see Warnings and Precautions (5.5)]. Metformin HCI

sinetic studies of metformin have been conducted in subjects with hepatic impairment [see Warnings and Precautions (5.5)]. Drug Interaction Studies pecific pharmacokinetic drug interaction studies with pioglitazone and metformin hydrochloride tablets have not been performed, although such studies have been conducted with the individual pioglitazone and metformin components.

Coadministered Drug

Pioglitazone Dosage Regimen (mg)*	Name and Dose Regimens	Change in AUC ⁺		Change in C _{max} †		
	Warfarin‡					
45 ma	Daily loading then maintenance doses	R-Warfarin	↓3%	R-Warfarin	↓2%	
(N = 12)	based PT and INR values Quick's Value = 35 ± 5%	S-Warfarin	↓1%	S-Warfarin	1%	
	Digoxin	Digoxin				
45 mg (N = 12)	0.200 mg twice daily (loading dose) then 0.250 mg daily (maintenance dose, 7 days)	115%	6	17%		
45 mg daily	Oral Contraceptive					
for 21 days	[Ethinyl Estradiol (EE) 0.035 mg plus	EE	↓11%	EE	↓13%	
(N = 35)	Norethindrone (NE) 1 mg] for 21 days	NE	13%	NE	↓7%	
45 mg	Fexofenadine					
(N = 23)	60 mg twice daily for 7 days	137%				
45 mg	Glipizide					
(N = 14)	5 mg daily for 7 days	↓3%		↓8%		
45 mg daily	Metformin					
for 8 days (N = 16)	1000 mg single dose on Day 8	↓3%	•	↓5%		
45 mg	Midazolam					
(N = 21)	7.5 mg single dose on Day 15	↓26%		↓26%		
45 mg	Ranitidine					
(N = 24)	150 mg twice daily for 7 days	1%	1	1%		
45 mg daily	Nifedipine ER					
for 4 days (N = 24)	30 mg daily for 4 days	↓13%	6	↓17%		
45 mg	Atorvastatin Calcium					
(N = 25)	80 mg daily for 7 days ↓14% ↓23%					
45 mg	Theophylline					
(N = 22)	400 mg twice daily for 7 days	12%		15%		
spectively.	s otherwise noted. It coadministered drug and no change = 0 ⁴ nically significant effect on prothrombin time	,, ,	id \downarrow indicate the	exposure increa	se and decrea	

Fable 19: Effect of Coadministered Drugs on Pioglitazone Systemic Exposu

	Pioglitazone				
Coadministered Drug and	Doos Dosimon	<u> </u>	Change		
Dosage Regimen	Dose Regimen (mg)*	Change in AUC ⁺	Change in C _{max} †		
Gemfibrozil 600 mg twice daily for 2 days (N = 12)	15 mg single dose	↑3.2-fold‡	16%		
Ketoconazole 200 mg twice daily for 7 days (N = 28)	45 mg	1€14	14%		
Rifampin 600 mg daily for5 days (N = 10)	30 mg single dose	↓54%	↓5%		
Fexofenadine 60 mg twice daily for 7 days (N = 23)	45 mg	1%	0%		
Ranitidine 150 mg twice daily for 4 days (N = 23)	45 mg	↓13%	↓16%		
Nifedipine ER 30 mg daily for 7 days (N = 23)	45 mg	↑5%	14%		
Atorvastatin Calcium 80 mg daily for 7 days (N = 24)	45 mg	↓24%	↓31%		
Theophylline 400 mg twice daily for 7 days (N = 22)	45 mg	↓4%	↓2%		
Topiramate 96 mg twice daily for 7 days [§] (N = 26)	30 mg§	↓15%1	0%		

*Daily for 7 days unless otherwise noted

Vean ratio (with/without coadministered drug and no change = 1-fold) % change (with/without coadministered drug and no change = 0%); vmbols of \uparrow and \downarrow indicate the exposure increase and decrease, respectively The absolute bioavailability of a 500 mg metformin tablet given under fasting conditions is approximately 50 to 60%. Studies using single +The half-life of pioglitazone increased from 8.3 hours to 22.7 hours in the presence of gemfibrozil *(see Dosage and Administration (2.3)*, The about both and the programment of the programme

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin*		Mean Ratio oadministered drug) :t = 1.00	
			AUC [†]	C _{max}	
No dosing adjustments rec	quired for the following:				
Glyburide	5 mg	500 mg§	0.98 [‡]	0.99 [‡]	
Furosemide	40 mg	850 mg	1.09‡	1.22 [‡]	
Nifedipine	10 mg	850 mg	1.16	1.21	
Propranolol	40 mg	850 mg	0.90	0.94	
Ibuprofen	400 mg	850 mg	1.05 [‡]	1.07 [‡]	
Drugs that are eliminated by renal tubular secretion may increase the accumulation of metformin [see Warnings and Precautions (5), Drug Interactions (7)].					
Cimetidine	400 mg	850 mg	1.40	1.61	
Carbonic anhydrase inhibitors may cause metabolic acidosis: [see Warnings and Precautions (5), Drug Interactions (7)].					

1.251

100 mg[¶] 500 mg¶ Topiramate $^{\dagger}AUC = AUC_{0,10}$

*Ratio of arithmetic mean SMetformin HCI extended-release tablets, 500 mg.

"At steady state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours;

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.00		
			AUC [†]	C _{max}	
dosing adjustments re	equired for the following:				
yburide	5 mg	500 mg§	0.78‡	0.63‡	
rosemide	40 mg	850 mg	0.87 [‡]	0.69 [‡]	
edipine	10 mg	850 mg	1.10 [§]	1.08	
opranolol	40 mg	850 mg	1.01§	0.94	
ıprofen	400 mg	850 mg	0.971	1.011	
netidine	400 mg	850 mg	0.95§	1.01	
C = AUC _{0 to ∞}	, p-value of difference <0.05.	ngle doses.			

Ratio of arithmetic means

13 NONCLINICAL TOXICOLOGY

13.1Carcinogenesis, Mutagenesis, Impairment of Fertility Pioglitazone and metformin hydrochloride tablets

No animal studies have been conducted with pioglitazone and metformin hydrochloride. The following data are based on findings in studies performed with pioglitazone or metformin individually. two year carcinogenicity study was conducted in male and female rats at oral doses up to 63 mg/kg (approximately 14 times the

maximum recommended human oral dose of 45 mg based on mg/m²). Drug-induced tumors were not observed in any organ except for decreases from baseline were generally greater for females than for males (average mean difference in HbA1c 0.5%). Because therapy should the urinary bladder of male rats. Benign and/or malignant transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m²). Urinary calculi with subsequent irritation and pyperplasia were postulated as the mechanism for bladder tumors observed in male rats. A two year mechanistic study in male rats utilizing ietary acidification to reduce calculi formation was completed in 2009. Dietary acidification decreased but did not abolish the hyperplas changes in the bladder. The presence of calculi exacerbated the hyperplastic response to pioglitazone but was not considered the primary

The relevance to humans of the bladder findings in the male rat cannot be excluded A two year carcinogenicity study was also conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11 times the

mum recommended human oral dose based on mg/m²). No drug-induced tumors were observed in any organ. Pioglitazone HCI was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, a mammalian cell forward gene mutation assay (CHO/HPRT and AS52/XPRT), an in vitro cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay, No adverse effects upon fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone HCl daily prior to and

throughout mating and gestation (approximately nine times the maximum recommended human oral dose based on mg/m²). Metformin HCI Long-term carcir 900 mg/kg/day.

oral dose based on mg/m²)

14 CLINICAL STUDIES

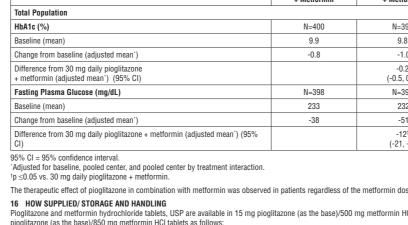
treated with pioglitazone and metformin hydrochloride tablets compared to either pioglitazone or metformin alone (see Table 22). Mellitus Inadequately Controlled with Diet and Exercise

Parameter	Hydro 1
HbA1c (%)	
Baseline (mean)	
Change from Baseline (adjusted mean*)	
Difference between pioglitazone and metformin hydrochloride tablets (adjusted mean*) 95% Confidence Interval	
% of patients with HbA1c <27%	
Fasting Plasma Glucose (mg/dL)	
Baseline (mean)	
Change from Baseline (adjusted mean*)	
Difference between pioglitazone and metformin hydrochloride tablets (adjusted mean*) 95% Confidence Interval	
 *Adjusted for baseline. †p ≤0.05 vs pioglitazone and metformin hydrochloride t 	ablets.
14.2 Patients Previously Treated with Metformin	o motfor

Pharmacology (12.3)]. metformin, either alone or in combination with another antidiabetic agent. All other antidiabetic agents were withdrawn at least three weeks prior to starting study treatment.

and FPG at endpoint compared to placebo add-on to metformin (see Table 23). Table 23: Glycemic Parameters in a 16 Week Placebo-Controlled, Add-on to Metformin Tria

Total Population
HbA1c (%)
Baseline (mean)
Change from baseline (adjusted mean')
Difference from placebo + metformin (adjusted mean') 95% Confidence Interval
Fasting Plasma Glucose (mg/dL)
Baseline (mean)
Change from baseline (adjusted mean [*])
Difference from placebo + metformin (adjusted mean`) 95% Confidence Interval
Adjusted for baseline, pooled center, and pooled center by trea $p \leq 0.05$ vs placebo + metformin.
n the second trial, 827 patients were randomized to receive e heir current metformin regimen. The mean reduction from baseline 5 mg dose <i>(see Table 24)</i> . The mean reduction from baseline 5 mg dose.
able 24: Glycemic Parameters in a 24 Week Add-on to Metf



pioglitazone (as the base)/850 mg metformin HCI tablets as follows "1280" on other side, available in: Bottles of 60 Bottles of 180

Bottles of 500 Bottles of 1000 15 mg/850 mg tablet: white to off-white colored, caps '1281" on other side, available in: Bottles of 60 Bottles of 180

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 ner tightly closed, and protect from moistur 17 PATIENT COUNSELING INFORMATION Advise the patient to read the FDA-approved patient labeling (Medication Guide)

- tablets to immediately report these symptoms to their healthcare provider. [see Warnings and Precautions (5.1)].
- malaise, unusual somnolence, or other nonspecific symptoms occur. receiving pioglitazone and metformin hydrochloride tablets

Bottles of 500

Bottles of 750

- unction has been confirmed to be normal.
- Warnings and Precautions (5.3)
- advice if they experience signs or symptoms of liver injury (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine) [see Warnings and Precautions (5.5)]. treatment as these may be due to bladder cancer [see Warnings and Precautions (5.6)]. Fractures: Inform female patients about the risk of fractures while taking pioglitazone and metfic
- nformation on factors that may contribute to fracture risk [see Warnings and Precautions (5.7)] ophthalmologist if they experience symptoms of macular edema [see Warnings and Precautions (5.8)].
- pioglitazone and metformin hydrochloride tablets [see Warnings and Precautions (5.9)]. (8.3)1
- Missed Dosage: Instruct patients if a dose is missed, not to double their next dose Trademarks are the property of their respective owners.

Pioglitazone and Metformin Hydrochloride Tablets	COUNTRY : US	LOCATION : Indrad			Supersedes A/W No.:	
Outsert	NO. OF COLORS: 1	REMARK :			V. No. : 01	
Back Side	PANTONE SHADE NOS.:	SUBSTRATE : 40 g/m2 Bible Paper				
8099813	Black	Activities	Department	Name	Signature	Date
640 x 510		Prepared By	Pkg. Dev.			
S/S		Reviewed By	Pkg. Dev.			
07-03-2025	Font Size 6 pt_Med. 10 pt	Approved By	Quality			

ar code and adjacent text must be visible on folded leaflet.

These details can be moved by printed to arrange pharma code/ Bar code and adjacent text visible on folded leaflet.

nicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times a human daily dose of 2000 mg of the metformin component of pioglitazone and metformin hydrochloride tablets based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential In patients with decreased renal function, the plasma and blood t₁₀ of metformin is prolonged and the renal clearance is decreased [see observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with There was no evidence of mutagenic potential of metformin in the following in vitro tests: Ames test (S. typhimurium), gene mutation test mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately

Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with pioglitazone HCI (approximately 11, one, and two times the maximum recommended human oral dose for mice, rats, and dogs, respectively, based on mg/m²). In one year rat study, drug-related early death due to apparent heart dysfunction occurred at an oral dose of 160 mg/kg/day (approximately 35 times the maximum recommended human oral dose based on mg/m²). Heart enlargement was seen in a 3 week study in monkeys at oral doses of 8.9 mg/kg and above (approximately four times the maximum recommended human oral dose based on mg/m²), but not in a 52 week study at oral doses up to 32 mg/kg (approximately 13 times the maximum recommended human

 $14.1 \ \ {\rm Patients} \ {\rm Who} \ {\rm Have} \ {\rm Inadequate} \ {\rm Glycemic} \ {\rm Control} \ {\rm with} \ {\rm Diet} \ {\rm and} \ {\rm Exercise} \ {\rm Alone}$ 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

Table 22: Glycemic Parameters in 24 Week Study of Pioglitazone and Metformin Hydrochloride Tablets in Patients with Type 2 Diabetes Treatment Group

Pioglitazone and Metformin Hydrochloride Tablets 15/850 mg Twice Daily	Pioglitazone 15 mg Twice Daily	Metformin 850 mg Twice Daily
N=188	N=162	N=193
8.9	8.7	8.7
-1.8	-1.0	-1.0
	0.9† (0.5, 1.2)	0.8 [†] (0.5, 1.2)
64	47	39
N=196	N=176	N=202
177	171	171
-40	-22	-25
	18† (8, 28)	15† (6, 25)

The efficacy and safety of pioglitazone as add-on to metformin therapy have been established in two clinical studies [see Clinical The two clinical trials testing pioglitazone as add-on to metformin therapy included patients with type 2 diabetes mellitus on any dose of

In the first trial, 328 patients were randomized to receive either 30 mg of pioglitazone or placebo once daily for 16 weeks in addition to their current metformin regimen. Treatment with pioglitazone as add-on to metformin produced statistically significant improvements in HbA1c

led, Add-on to Metformin Trial			
	Placebo + Metformin	Pioglitazone 30 mg + Metformin	
	N=153	N=161	
	9.8	9.9	
	0.2	-0.6	
		-0.8† (-1.2, -0.5)	
	N=157	N=165	
	260	254	
	-5	-43	
		-38† (-49, -26)	
ment interaction			

either 30 mg or 45 mg of pioglitazone once daily for 24 weeks in addition to asseline at Week 24 in HbA1c was 0.8% for the 30 mg dose and 1.0% for the ne at Week 24 in FPG was 38 mg/dL for the 30 mg dose and 51 mg/dL for the formin Study

	Pioglitazone 30 mg + Metformin	Pioglitazone 45 mg + Metformin
	N=400	N=398
	9.9	9.8
	-0.8	-1.0
		-0.2 (-0.5, 0.1)
	N=398	N=399
	233	232
	-38	-51
mean') (95%		-12 [†] (-21, -4)

Pioglitazone and metformin hydrochloride tablets, USP are available in 15 mg pioglitazone (as the base)/500 mg metformin HCl and 15 mg 15 mg/500 mg tablet: white to off-white colored, capsule shaped, biconvex, film coated tablets debossed with "15/500" on one side and

- NDC 13668-280-60 NDC 13668-280-33 NDC 13668-280-05 NDC 13668-280-10 shaped, biconvex, film coated tablets debossed with "15/850" on one side and
- NDC 13668-281-60 NDC 13668-281-33 NDC 13668-281-08 NDC 13668-281-49

Congestive Heart Failure: Inform patients of the signs and symptoms of heart failure. Instruct patients who experience an unusually rapid increase in weight or edema, shortness of breath, or other symptoms of heart failure while on pioglitazone and metformin hydrochloride Lactic Acidosis: Explain to patients the risks of lactic acidosis, its symptoms and conditions that predispose to its development, as noted in the Warnings and Precautions (5.2) section. Advise patients to discontinue pioplitazone and metformin hydrochloride tablets nediately and to promptly notify their healthcare professional if unexplained hyperventilation, myalgia, gastrointestinal symptoms, provider if you: Counsel patients against excessive alcohol intake and inform patients about the importance of regular testing of renal function while Inform patients about the importance of regular testing of renal function and hematologic parameters when receiving treatment with Instruct patients to inform their doctor that they are taking pioglitazone and metformin hydrochloride tablets prior to any surgical or adiological procedure, as temporary discontinuation of pioglitazone and metformin hydrochloride tablets may be required until renal Edema: Inform patients that pioglitazone and metformin hydrochloride tablets use can lead to new-onset or worsening of edema. uct patients to immediately report symptoms of rapid weight increase or worsening edema to their healthcare provider [see

 <u>Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues</u>: Inform patients that the risk of hypoglycemia is increased when pioglitazone and metformin hydrochloride tablets is used with insulin or insulin secretagogues (such as a sulfonylurea). Educate patients on the signs and symptoms of hypoglycemia [see Warnings and Precautions (5.4)]. <u>Hepatic Effects</u>: Instruct patients to promptly stop taking pioglitazone and metformin hydrochloride tablets and seek immediate medical

Urinary Bladder Tumors: Advise patients to promptly report any hematuria, dysuria or urinary urgency that develops or increases during

Macular Edema: Educate patients on the signs and symptoms of macular edema and advise them to seek medical attention from an

Vitamin B12 Levels: Inform patients about the importance of obtaining regular hematological laboratory monitoring while receiving Females of Reproductive Age: Inform female patients that treatment with pioglitazone and metformin hydrochloride tablets may result in an unintended pregnancy in some premenopausal anovulatory females due to its effect on ovulation [see Use in Specific Populations

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. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment. If you have any questions about pioglitazone and metformin hydrochloride tablets, ask your healthcare provider 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:

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.

Before you start taking pioglitazone and metformin hydrochloride tablets: Tell your healthcare provider if you have ever had heart failure or have problems with your kidneys

- Call your healthcare provider right away if you have any of the following: increasing shortness of breath or trouble breathing, especially when you lie down an unusually fast increase in weight
 - swelling or fluid retention, especially in the ankles or legs unusual tiredness
- These may be symptoms of heart failure.
- Lactic acidosis. Metformin, one of the medicines in pioglitazone and metformin hydrochloride tablets, can cause a rare but serious condition called lactic acidosis (a buildup of an acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

Stop taking pioglitazone and metformin hydrochloride tablets and call your healthcare provider right away if you have any of the following symptoms, which could be signs of lactic acidosis:

- feel very weak or tired have unusual (not normal) muscle pain
- have trouble breathing
- have unusual sleepiness or sleep longer than usual • have unexplained stomach or intestinal problems with nausea, vomiting, or diarrhea
- feel cold, especially in your arms and legs
- feel dizzy or lightheaded have a slow or irregular heartbeat

Most people who have had lactic acidosis with metformin have other things that, combined with the metformin, led to the lactic acidosis. Tell your healthcare provider if you have any of the following, because you have a higher chance for getting lactic acidosis with pioglitazone and metformin hydrochloride tablets if you: have severe kidney problems or your kidneys are affected by certain x-ray tests

- that use injectable dye.
- have liver problems drink alcohol very often, or drink a lot of alcohol in short-term ("binge" drinking) get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids have surgerv
- have a heart attack, severe infection, or stroke are 65 years of age or older

The best way to keep from having a problem with lactic acidosis from metformin is to tell your healthcare provider if you have any of the problems in the list above. Your healthcare ovider mav decide to stop vour pioal while if you have any of these things.

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

- Pioglitazone and metformin hydrochloride tablets are prescription medicine that contains 2 diabetes medicines, pioglitazone (ACTOS) and metformin hydrochloride (GLUCOPHAGE). Pioglitazone and metformin hydrochloride tablets are used along with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes.
- Pioglitazone and metformin hydrochloride tablets are not for people with type 1 diabetes. Pioglitazone and metformin hydrochloride tablets are not for people with diabetic ketoacidosis (increased ketones in your blood or urine).

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

Who should not take pioglitazone and metformin hydrochloride tablets? See "What is the most important information I should know about pioglitazone and metformin hydrochloride tablets?"

- Do not take pioglitazone and metformin hydrochloride tablets if you:
- have severe heart failure have severe kidney problems
- have a condition called acute or chronic metabolic acidosis, including diabetic ketoacidosis

are allergic to pioglitazone, metformin, or any of the ingredients in pioglitazone and metformin hydrochloride tablets or have had a serious allergic (hypersensitivity) reaction to pioglitazone or metformin. See the end of this Medication Guide for a complete list of ingredients in pioglitazone and metformin hydrochloride tablets. Symptoms of a serious allergic reaction to pioglitazone and metformin hydrochloride tablets may include:

- swelling of your face, lips, throat
 difficulty with swallowing and other areas on skin or your breathing
- skin rash, itching, flaking raised, red areas on your skin (hives) or peeling
- If you have these symptoms, stop taking pioglitazone and metformin hydrochloride tablets and contact your healthcare provider or go to the nearest hospital emergency room right away.

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

What should I tell my healthcare provider before taking pioglitazone and metformin hydrochloride tablets? Before you take pioglitazone and metformin hydrochloride tablets, tell your healthcare

- have heart failure
- have kidney or liver problems
- are going to have dye injected into a vein for an x-ray, CAT scan, heart study, or other type of scanning
- will be undergoing a surgical procedure drink a lot of alcohol (all the time or short binge drinking)
- have type 1 ("juvenile") diabetes or had diabetic ketoacidosis have a type of diabetic eye disease that causes swelling in the back of the eye (macular
- have low levels of vitamin B₁₂ in your blood
- have or have had cancer of the bladder
- are pregnant or plan to become pregnant. It is not known if pioglitazone and metformin hydrochloride tablets can harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant about the best way to control your blood glucose levels while pregnant
- are a woman who has not gone through menopause (premenopausal), who does **not have periods regularly or at all.** Pioglitazone and metformin hydrochloride tablets may increase your chance of becoming pregnant. Talk to your healthcare provider about birth control choices while taking pioglitazone and metformin hydrochloride tablets. Tell your healthcare provider right away if you become pregnant while taking pioglitazone and metformin hydrochloride tablets
- are breastfeeding or plan to breastfeed. It is not known if pioglitazone and metformin hydrochloride passes into your milk and if it can harm your baby. Talk to your healthcare provider about the best way to control your blood glucose levels while breastfeeding Tell your healthcare provider 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 healthcare provider 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. Pioglitazone and metformin hydrochloride tablets may affect the way other medicines work, and other medicines may affect how pioglitazone and metformin hydrochloride tablets work. Contact your healthcare provider before you start or stop other types of medicines.

- How should I take pioglitazone and metformin hydrochloride tablets?
- Take pioglitazone and metformin hydrochloride tablets exactly as your healthcare provider tells you to take it Your healthcare provider may need to change your dose of pioglitazone and metformin hydrochloride tablets. Do not change your pioglitazone and metformin hydrochloride tablets dose unless your healthcare provider tells you to
- Take pioglitazone and metformin hydrochloride tablets with meals to lower your chance of an upset stomach If you miss a dose of pioglitazone and metformin hydrochloride tablets, take your next
- dose as prescribed unless your healthcare provider tells you differently. Do not take two doses at one time the next day If you take too much pioglitazone and metformin hydrochloride tablets, call your
- healthcare provider or go to the nearest hospital emergency room right away If your body is under stress such as from a fever, infection, accident, or surgery, the dose of your diabetes medicines may need to be changed. Call your healthcare provider right away
- Stay on your diet and exercise programs and test your blood sugar regularly while taking pioglitazone and metformin hydrochloride tablets • Your healthcare provider should do certain blood tests before you start and while you take pioglitazone and metformin hydrochloride tablets
- Your healthcare provider should also do hemoglobin A1C testing to check how well your blood sugar is controlled with pioglitazone and metformin hydrochloride tablets Your healthcare provider should check your eyes regularly while you take pioglitazone and metformin hydrochloride tablets

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

- See "What is the most important information I should know about pioglitazone and metformin hydrochloride tablets?" Low blood sugar (hypoglycemia). If you take pioglitazone and metformin hydrochloride tablets with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take pioglitazone and metformin hydrochloride tablets. Signs and symptoms of low blood sugar may include:
- fast heartbeat shaking or feeling jittery sweating • change in vision hunger headache change in mood confusion dizziness
- **Liver problems.** Call your healthcare provider right away or go to the nearest hospital emergency room if you have unexplained symptoms such as:
- nausea or vomiting stomach pain
- unusual or unexplained tiredness
- loss of appetite dark urine
- yellowing of your skin or the whites of your eyes **Bladder tumors.** There may be an increased chance of having bladder cancer when you take pioglitazone and metformin hydrochloride tablets. You should not take pioglitazone and metformin hydrochloride tablets if you are receiving treatment for bladder cancer. Tell your healthcare provider right away if you have any of the following
- symptoms of bladder cancer:
- blood or a red color in vour urine an increased need to urinate
- pain while you urinate
- Broken bones (fractures). Usually in the hand, upper arm, or foot in women. Talk to your healthcare provider for advice on how to keep your bones healthy Diabetic eye disease with swelling in the back of the eye (macular edema). Tell your
- healthcare provider right away if you have any changes in your vision. Your healthcare provider should check your eyes regularly Release of an egg from an ovary in a woman (ovulation) leading to pregnancy. Ovulation may happen when premenopausal women who do not have regular monthly
- periods take pioglitazone and metformin hydrochloride tablets. This can increase your chance of getting pregnant. Low vitamin B₁₂ (vitamin B₁₂ deficiency). Using metformin, one of the medicines in pioglitazone and metformin hydrochloride tablets for long periods of time may cause
- a decrease in the amount of vitamin B_{12} in your blood, especially if you have had low vitamin B₁₂ levels before. Your healthcare provider may do blood tests to check your vitamin B₁₂ levels. The most common side effects of pioglitazone and metformin hydrochloride tablets include:
- cold-like symptoms (upper respiratory tract infection) swelling (edema)
- diarrhea
- headache

hvdrochloride tablet

torrent

Manufactured by:

Manufactured for:

8099813

PHARMA

Torrent Pharmaceuticals LTD., India.

increased weight Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the side effects of pioglitazone and metformin hydrochloride tablets. For more information, ask your healthcare provider or pharmacist.

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

- How should I store pioglitazone and metformin hydrochloride tablets? Store pioglitazone and metformin hydrochloride tablets at 20° to 25° C (68° to 77°) F); excursions permitted to 15° to 30° C (59° to 86° F) [see USP Controlled Room
- Temperature1 • Keep pioglitazone and metformin hydrochloride tablets in the original container and protect from light.
- Keep the pioglitazone and metformin hydrochloride tablets bottle tightly closed and keep tablets dry.

Keep pioglitazone and metformin hydrochloride tablets and all medicines out of the reach of children. General information about the safe and effective use of pioglitazone and metformin

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

You can ask your healthcare provider or pharmacist for information about pioglitazone and

Active Ingredients: pioglitazone hydrochloride, USP and metformin hydrochloride, USP

Inactive Ingredients: croscarmellose sodium, hypromellose, magnesium stearate,

Revised: March 2025

to other people, even if they have the same symptoms you have. It may harm them.

What are the ingredients in pioglitazone and metformin hydrochloride tablets?

microcrystalline cellulose, polyethylene glycol, povidone, talc, and titanium dioxide

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

metformin hydrochloride tablets that is written for health professionals.

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For more information, call 1-800-912-9561.

Dispense with Medication Guide available at:

<u>https://torrentpharma.com/pi/usa/products/</u>

Torrent Pharma INC., Basking Ridge, NJ 07920.

