Averofage 15/500 mg F.C.T

Averofage 15/850 mg F.C.T

WARNING: CONGESTIVE HEART FAILURE AND LACTIC ACIDOSIS

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 *[see Warnings and Precautions] .*
- After initiation of pioglitazone and metformin hydrochloride tablets, and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea, and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of pioglitazone and metformin hydrochloride tablets must be considered *[see Warnings and Precautions] .*
- Pioglitazone and metformin hydrochloride tablets are not recommended in patients with symptomatic heart failure *[see Warnings and Precautions] .*
- 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 and Warnings and Precautions] .

Lactic Acidosis

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

INDICATIONS AND USAGE

Pioglitazone and metformin hydrochloride tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both pioglitazone and metformin is appropriate.

Important Limitations of Use

Pioglitazone exerts its antihyperglycemic effect only in the presence of endogenous insulin. Pioglitazone and metformin hydrochloride tablets should not be used to treat type 1 diabetes or diabetic ketoacidosis, as it would not be effective in these settings.

Use caution in patients with liver disease *[see Warnings and Precautions].*

DOSAGE AND ADMINISTRATION

1-Recommendations for All Patients

Pioglitazone and metformin hydrochloride tablets should be taken with meals to reduce the gastrointestinal side effects associated with metformin.

If therapy with a combination tablet containing pioglitazone and metformin is considered appropriate the recommended starting dose is:

15 mg/500 mg twice daily or 15 mg/850 mg once daily and gradually titrated, as needed, after assessing adequacy of therapeutic response and tolerability,

for patients with New York Heart Association (NYHA) Class I or Class II congestive heart failure: 15 mg/500 mg or 15 mg/850 mg once daily and gradually titrated, as needed, after assessing adequacy of therapeutic response and tolerability,

for patients inadequately controlled on metformin monotherapy: 15 mg/500 mg twice daily or 15 mg/850 mg once or twice daily (depending on the dose of metformin already being taken) and gradually titrated, as needed, after assessing adequacy of therapeutic response and tolerability,

for patients inadequately controlled on pioglitazone monotherapy: 15 mg/500 mg twice daily or 15 mg/850 mg once daily and gradually titrated, as needed, after assessing adequacy of therapeutic response and tolerability,

for patients who are changing from combination therapy of pioglitazone plus metformin as separate tablets: pioglitazone and metformin hydrochloride tablets should be taken at doses that are as close as possible to the dose of pioglitazone and metformin already being taken.

Pioglitazone and metformin hydrochloride tablets may be titrated up to a maximum daily dose of 45 mg of pioglitazone and 2550 mg of metformin.

Metformin doses above 2000 mg may be better tolerated given three times a day.

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

Liver tests (serum alanine and aspartate aminotransferases, alkaline phosphatase, and total bilirubin) should be obtained prior to initiating pioglitazone and metformin hydrochloride tablets. Routine periodic monitoring of liver tests during treatment with pioglitazone and metformin hydrochloride tablets is not recommended in patients without liver disease. Patients who have liver test abnormalities prior to initiation of pioglitazone and metformin hydrochloride tablets or who are found to have abnormal liver tests while taking pioglitazone and metformin hydrochloride tablets should be managed as described under Warnings and Precautions [see Warnings and Precautions and Clinical Pharmacology].

2-Recommendations for Use in Renal Impairment

Assess renal function prior to initiation of pioglitazone and metformin hydrochloride tablets and periodically thereafter.

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

Initiation of pioglitazone and metformin hydrochloride tablets in patients with an eGFR between 30 to 45 mL/min/1.73 m2is not recommended.

In patients taking pioglitazone and metformin hydrochloride tablets whose eGFR later falls below 45 mL/min/1.73 m2, assess the benefit risk of continuing therapy.

Discontinue pioglitazone and metformin hydrochloride tablets if the patient's eGFR later falls below 30 mL/min/1.73 m2[see Contraindications and Warnings and Precautions].

3-Concomitant Use with Strong CYP2C8 Inhibitors

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

4-Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue pioglitazone and metformin hydrochloride tablets at the time of, or prior to, an iodinated contrast imaging procedures in patients with eGFR between 30 and 60 mL/min/1.73 m2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra- arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart pioglitazone and metformin hydrochloride tablets if renal function is stable *[see Warnings and Precautions].*

CONTRAINDICATIONS

Initiation in patients with established NYHA Class III or IV heart failure *[see Boxed Warning]* . Severe renal impairment (eGFR below 30 mL/min/1.73 m2*[see Warnings and Precautions].*

Use in patients with known hypersensitivity to pioglitazone, metformin, or any other component of pioglitazone and metformin hydrochloride tablets.

Metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.

WARNINGS AND PRECAUTIONS

1-Congestive Heart Failure

Pioglitazone

Pioglitazone, like other thiazolidinediones, can cause dose-related fluid retention when used alone or in combination with other antidiabetic medications and is most common when pioglitazone is used in combination with insulin. Fluid retention may lead to or exacerbate congestive heart failure. Patients treated with pioglitazone and metformin hydrochloride should be observed for signs and symptoms of congestive heart failure. If congestive heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of pioglitazone and metformin hydrochloride must be considered [see Boxed Warning, Contraindications, and Adverse Reactions].

2-Lactic Acidosis

Metformin hydrochloride

Lactic Acidosis

There have been post-marketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (greater than 5 mmol/L), anion gap acidosis (without evidence of ketonuria

or ketonemia), and an increased lactate:pyruvate ratio;metformin plasma levels generally greater than 5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

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

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

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

Renal Impairment

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

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

Pioglitazone and metformin hydrochloride tablets are contraindicated in patients with an eGFR less than 30mL/min/1.73 m2. Initiation of pioglitazone and metformin hydrochloride tablets is not recommended in patients with eGFR between 30 to 45 mL/min/1.73 m2[see Contraindications] .

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

In patients taking pioglitazone and metformin hydrochloride tablets whose eGFR later falls below 45 mL/min/1.73 m2, assess the benefit and risk of continuing therapy.

Drug Interactions

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

Age 65 or Greater

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

Radiological Studies with Contrast

Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop pioglitazone and metformin hydrochloride tablets at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re- evaluate eGFR 48 hours after the imaging procedure, and restart pioglitazone and metformin hydrochloride tablets if renal function is stable.

Surgery and Other Procedures

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

Hypoxic States

Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia).

Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue pioglitazone and metformin hydrochloride tablets.

Excessive Alcohol Intake

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

Hepatic Impairment

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

3-Edema

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

Pioglitazone and metformin hydrochloride should be used with caution in patients with edema. Because thiazolidinediones, including pioglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, pioglitazone and metformin hydrochloride should be used with caution in patients at risk for congestive heart failure. Patients treated with pioglitazone and metformin hydrochloride should be monitored for signs and symptoms of congestive heart failure [see Boxed Warning, Warnings and Precautions, and Patient Counseling Information].

4-Hypoglycemia

Patients receiving pioglitazone and metformin hydrochloride in combination with insulin or other antidiabetic medications (particularly insulin secretagogues such as sulfonylureas) may be at risk for hypoglycemia. A reduction in the dose of the concomitant antidiabetic medication may be necessary to reduce the risk of hypoglycemia [see Drug Interactions]. Hypoglycemia can also occur when caloric intake is deficient or when strenuous exercise is not compensated by caloric supplement.

Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

5-Hepatic Effects

There have been postmarketing reports of fatal and nonfatal hepatic failure in patients taking pioglitazone, although the reports contain insufficient information necessary to establish the probable cause. There has been no evidence of drug-induced hepatotoxicity in the pioglitazone controlled clinical trial database to date [see Adverse Reactions].

Patients with type 2 diabetes may have fatty liver disease or cardiac disease with episodic congestive heart failure, both of which may cause liver test abnormalities, and they may also have other forms of liver disease, many of

which can be treated or managed. Therefore, obtaining a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) and assessing the patient is recommended before initiating pioglitazone and metformin hydrochloride therapy.

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

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (ALT greater than three times the upper limit of the reference range), pioglitazone and metformin hydrochloride treatment should be interrupted and investigation done to establish the probable cause. Pioglitazone and metformin hydrochloride should not be restarted in these patients without another explanation for the liver test abnormalities.

Patients who have serum ALT greater than three times the reference range with serum total bilirubin greater than two times the reference range without alternative etiologies are at risk for severe drug- induced liver injury, and should not be restarted on pioglitazone and metformin hydrochloride. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with pioglitazone and metformin hydrochloride can be used with caution.

6- Urinary Bladder Tumors

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

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

7- Fractures

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 versus placebo. The risk of fracture should be considered in the care of patients, especially female patients, treated with pioglitazone and metformin hydrochloride and attention should be given to assessing and maintaining bone health according to current standards of care.

8-Macular Edema

Macular edema has been reported in postmarketing experience in diabetic patients who were taking pioglitazone or another thiazolidinedione. Some patients presented with blurred vision or decreased visual acuity, but others were diagnosed on routine ophthalmologic examination.

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

Patients with diabetes should have regular eye exams by an ophthalmologist according to current standards of care. Patients with diabetes who report any visual symptoms should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings [see Adverse Reactions].

9-Vitamin B12 Levels

A decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the

B12-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on pioglitazone and metformin

hydrochloride tablets and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. In these patients, routine serum vitamin B12 measurements at two- to three-year intervals may be useful.

10-Macrovascular Outcomes

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

ADVERSE REACTIONS

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

- Congestive heart failure [see Boxed Warning and Warnings and Precautions Lactic acidosis [see Boxed Warning and Warnings and Precautions].
- Edema [see Warnings and Precautions].
- Fractures [see Warnings and Precautions].

1-Clinical Trials Experience

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

Pioglitazone

Adverse Events Reported at an Incidence >5% and More Commonly in Patients Treated with Pioglitazone

Upper Respiratory Tract Infection – Headache – Sinusitis – Myalgia- Pharyngitis.

Adverse Events Reported in >5% of Patients and More Commonly in Patients Treated with Pioglitazone + Metformin

Edema – Headache.

Adverse Events Reported in >5% of Patients and More Commonly in Patients Treated with Pioglitazone 45 mg + Metformin than in Patients Treated with Pioglitazone 30 mg + Metformin

Upper Respiratory Tract Infection – Edema- Headache- Weight Increased.

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

Common Adverse Events: Pioglitazone and Metformin Hydrochloride Tablets Administered Twice Daily

Diarrhea – Headache.

Common Adverse Events: PROactive Trial

Incidence and Types of Adverse Events Reported in >5% of Patients Treated with Pioglitazone and More Commonly

Hypoglycemia- Edema- Cardiac Failure - Pain in Extremity - Back Pain - Chest Pain.

Metformin hydrochloride

Most Common Adverse Reactions (>5.0%) in a Placebo-Controlled Clinical Study of Metformin Monotherapy*

Diarrhea - Nausea/Vomiting – Flatulence – Asthenia – Indigestion - Abdominal Discomfort – Headache.

Laboratory Abnormalities

Hematologic Effects

Pioglitazone may cause decreases in hemoglobin and hematocrit. These changes primarily occurred within the first 4 to 12 weeks of therapy and remained relatively constant thereafter. These changes may be related to increased plasma volume associated with pioglitazone therapy and are not likely to be associated with any clinically significant hematologic effects.

Vitamin B12 Concentrations

Metformin may lower serum vitamin B12 concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on pioglitazone and metformin hydrochloride and any apparent abnormalities should be appropriately investigated and managed [see Warnings and Precautions].

Creatine Phosphokinase

During protocol-specified measurement of serum creatine phosphokinase (CPK) in pioglitazone clinical trials, an isolated elevation in CPK to greater than 10 times the upper limit of the reference range was noted in nine (0.2%) patients treated with pioglitazone (values of 2150 to 11400 IU/L) and in no comparator- treated patients. Six of these nine patients continued to receive pioglitazone, two patients were noted to have the CPK elevation on the last day of dosing, and one patient discontinued pioglitazone due to the elevation. These elevations resolved without any apparent clinical sequelae.

The relationship of these events to pioglitazone therapy is unknown.

2- Postmarketing Experience

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

Pioglitazone

- New onset or worsening diabetic macular edema with decreased visual acuity *[see Warnings and Precautions]* .
- Fatal and nonfatal hepatic failure *[see Warnings and Precautions]* .

Postmarketing reports of congestive heart failure have been reported in patients treated with pioglitazone, both with and without previously known heart disease and both with and without concomitant insulin administration.

In postmarketing experience, there have been reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such increases should be assessed for fluid accumulation and volume- related events such as excessive edema and congestive heart failure *[see Boxed Warning and Warnings and Precautions].*

Metformin

Cholestatic, hepatocellular, and mixed hepatocellular liver injury.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorization of the medicinal product is Important. It allows continued monitoring of the benefit/risk balance of the medicinal Product. Healthcare professionals are asked to report any suspected adverse reactions via:

E-mail:

avs@averroespharma.net

regi@averroes-eg.com

Or on the following address:

Block No 6048, 6th industrial zone Sadat city, Egypt. Tel: 0482630201/2, Fax: 0482630203

55 Hafez badawy street Nasr city, Egypt.

Also you can report via:

Egyptian Pharmaceutical Vigilance Center (EPVC)

21 Abd El Aziz Al Soud Street. El-Manial, Cairo, Egypt.

E-mail: pv.center@eda.mohp.gov.eg

Fax Number: +2 02 23684194

Telephone: +2 02 (23648046, 23640368, 23684381, 23684288), Extension No. 1303

DRUG INTERACTIONS

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 (t1/2) of pioglitazone. Therefore, the maximum recommended

dose of pioglitazone is 15 mg daily if used in combination with gemfibrozil or other strong CYP2C8 inhibitors [see Dosage and Administration and Clinical Pharmacology].

2-CYP2C8 Inducers

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

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.

4-Drugs that Reduce Metformin Clearance

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

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.

6-Insulin Secretagogues or Insulin

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

If hypoglycemia occurs in a patient coadministered pioglitazone and metformin hydrochloride and insulin, the dose of insulin should be decreased by 10% to 25%. Further adjustments to the insulin dose should be individualized based on glycemic response.

7-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.

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.

USE IN SPECIFIC POPULATIONS

1-Pregnancy Risk Summary

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

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

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

Data

Human Data

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

2-Lactation Risk Summary

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

Data

Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% 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.

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.

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-Geriatric Use Pioglitazone

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

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

Metformin hydrochloride

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

6-Renal Impairment

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

7-Hepatic Impairment

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

OVERDOSAGE

Pioglitazone

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

Metformin hydrochloride

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

CLINICAL PHARMACOLOGY

1-Mechanism of Action

Pioglitazone and metformin hydrochloride tablets combine two antidiabetic medications with different mechanisms of action to improve glycemic control in adults with type 2 diabetes: pioglitazone, a thiazolidinedione, and metformin hydrochloride, a biguanide. Thiazolidinediones are insulin-sensitizing agents that act primarily by enhancing peripheral glucose utilization, whereas biguanides act primarily by decreasing endogenous hepatic glucose production.

Pioglitazone

Pioglitazone is a thiazolidinedione that depends on the presence of insulin for its mechanism of action. Pioglitazone decreases insulin resistance in the periphery and in the liver resulting in increased insulin- dependent glucose disposal and decreased hepatic glucose output. Pioglitazone is not an insulin secretagogue. Pioglitazone is an agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

In animal models of diabetes, pioglitazone reduces the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states such as type 2 diabetes. The metabolic changes produced by pioglitazone result in increased responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance.

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

Metformin hydrochloride

Metformin hydrochloride improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not produce hypoglycemia in either patients with type 2 diabetes or healthy subjects [except in specific circumstances, see Warnings and Precautions] 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.

2-Pharmacodis Pioglitazone

Clinical studies demonstrate that pioglitazone improves insulin sensitivity in insulin- resistant patients. Pioglitazone enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal and improves hepatic sensitivity to insulin. In patients with type 2 diabetes, the decreased insulin resistance produced by pioglitazone results in lower plasma glucose concentrations, lower plasma insulin concentrations, and lower HbA1c values. In controlled clinical trials, pioglitazone had an additive effect on glycemic control when used in combination with a sulfonylurea, metformin, or insulin.

Patients with lipid abnormalities were included in clinical trials with pioglitazone. Overall, patients treated with pioglitazone had mean decreases in serum triglycerides, mean increases in HDL cholesterol, and no consistent mean changes in LDL and total cholesterol. There is no conclusive evidence of macrovascular benefit with pioglitazone or any other antidiabetic medication *[see Warnings and Precautions and Adverse Reactions].*

3-Pharmacokinetics 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 (Cmax) of both the pioglitazone and the metformin component following a single dose of the combination tablet were bioequivalent to

pioglitazone 15 mg concomitantly administered with metformin hydrochloride (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.

Pioglitazone

Following once-daily administration of pioglitazone, steady-state serum concentrations of both pioglitazone and its major active metabolites, M-III (keto derivative of pioglitazone) and M-IV (hydroxyl derivative of pioglitazone), are achieved within 7 days. At steady-state, M-III and M-IV reach serum concentrations equal to or greater than that of pioglitazone. At steady-state, in both healthy volunteers and patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the peak total pioglitazone serum concentrations (pioglitazone plus active metabolites) and 20% to 25% of the total AUC.

Cmax, AUC, and trough serum concentrations (C_{min}) for pioglitazone and M-III and M-IV, increased proportionally with administered doses of 15 mg and 30 mg per day.

Following oral administration of pioglitazone, T_{max} of pioglitazone was within two hours. Food delays the Tmax to three to four hours, but does not alter the extent of absorption (AUC).

Metformin hydrochloride

The absolute bioavailability of a 500 mg metformin tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin tablets of 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. At usual clinical doses and dosing schedules of metformin, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 mcg/mL. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Food decreases the rate and extent of metformin absorption, as shown by a 40% lower mean Cmax, a 25% lower AUC, and a 35 minute prolongation of T_{max} following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Pioglitazone

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

Metformin hydrochloride

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

Metabolism

Pioglitazone

Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-III and M-IV are the major circulating active metabolites in humans.

In vitro data demonstrate that multiple CYP isoforms are involved in the metabolism of pioglitazone which include CYP2C8 and, to a lesser degree, CYP3A4 with additional contributions from a variety of other isoforms, including the mainly extrahepatic CYP1A1. In vivo study of pioglitazone in combination with gemfibrozil, a strong CYP2C8 inhibitor, showed that pioglitazone is a CYP2C8 substrate *[see Dosage and Administration and Drug Interactions].* Urinary 6ß hydroxycortisol/cortisol ratios measured in patients treated with pioglitazone showed that pioglitazone is not a strong CYP3A4 enzyme inducer.

Metformin hydrochloride

Intravenous single-dose studies in healthy subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Excretion and Elimination

Pioglitazone

Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.

The mean serum half-life (t1/2) of pioglitazone and its metabolites (M-III and M-IV) range from three to seven hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be five to seven L/hr.

Metformin hydrochloride

Renal clearance is approximately 3.5 times greater than creatinine clearance (CLcr), which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with

a plasma elimination t1/2 of approximately 6.2 hours. In blood, the elimination t1/2 is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Specific Populations Renal Impairment Pioglitazone

The serum elimination half-life of pioglitazone, M-III and M-IV remains unchanged in patients with moderate (CLcr 30 to 50 mL/min) and severe (CLcr <30 mL/min) renal impairment when compared to subjects with normal renal function. Therefore, no dose adjustment in patients with renal impairment is required.

Metformin hydrochloride

In patients with decreased renal function, the plasma and blood t1/2 of metformin is prolonged and the renal clearance is decreased *[see Dosage and Administration, Contraindications and Warnings and Precautions].*

Hepatic Impairment

Pioglitazone

Compared with healthy controls, subjects with impaired hepatic function (Child-Turcotte- Pugh Grade B/C) have an approximate 45% reduction in pioglitazone and total pioglitazone (pioglitazone, M-III, and M-IV) mean Cmax but no change in the mean AUC values. Therefore, no dose adjustment in patients with hepatic impairment is required.

There are postmarketing reports of liver failure with pioglitazone and clinical trials have generally excluded patients with serum ALT >2.5 times the upper limit of the reference range. Use pioglitazone and metformin hydrochloride with caution in patients with liver disease [see Warnings and Precautions].

Metformin hydrochloride

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

Geriatric Patients

Pioglitazone

In healthy elderly subjects, Cmax of pioglitazone was not significantly different, but AUC values were approximately 21% higher than those achieved in younger subjects. The mean t1/2 of pioglitazone was also prolonged in elderly subjects (about ten hours) as compared to younger subjects (about seven hours). These changes were not of a magnitude that would be considered clinically relevant.

Metformin hydrochloride

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total CL/F is decreased, the t1/2 is prolonged, and Cmax is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatrics

Pioglitazone

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

Metformin hydrochloride

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

Gender

Pioglitazone

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

Metformin hydrochloride

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

Ethnicity

Pioglitazone

Pharmacokinetic data among various ethnic groups are not available.

Metformin hydrochloride

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51), and Hispanics (n=24).

Drug-Drug Interactions

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

Pioglitazone

Table . Effect of Pioglitazone Coadministration on Systemic Exposure of Other Drugs					
	Coadministered Drug				
Pioglitazone Dosage Regimen (mg)*	**Name and Dose Regimens**	**Change in AUC†**		**Change in Cmax†**	
45 mg (N = 12)	**Warfarin‡**				
	Daily loading then maintenance doses based PT and INR values Quick's Value = 35 ± 5%	R-Warfarin	↓3%	R-Warfarin	↓2%
		S-Warfarin	↓1%	S-Warfarin	↑1%
45 mg (N = 12)	**Digoxin**				
	0.200 mg twice daily (loading dose) then 0.250 mg daily (maintenance dose, 7 days)	↑15%		↑17%	
45 mg daily for 21 days (N = 35)	**Oral Contraceptive**				
	[Ethinyl Estradiol (EE) 0.035 mg plus Norethindrone (NE) 1 mg] for 21 days	EE	↓11%	EE	↓13%
		NE	↑3%	NE	↓7%
45 mg (N = 23)	**Fexofenadine**				
	60 mg twice daily for 7 days	↑30%		↑37%	
45 mg (N = 14)	**Glipizide**				
	5 mg daily for 7 days	↓3%		↓8%	
45 mg daily for 8 days (N = 16)	**Metformin**				
	1000 mg single dose on Day 8	↓3%		↓5%	
45 mg (N = 21)	**Midazolam**				
	7.5 mg single dose on Day 15	↓26%		↓26%	
45 mg (N = 24)	**Ranitidine**				
	150 mg twice daily for 7 days	↑1%		↓1%	
45 mg daily for 4 days (N = 24)	**Nifedipine ER**				
	30 mg daily for 4 days	↓13%		↓17%	
45 mg (N = 25)	**Atorvastatin Ca**				
	80 mg daily for 7 days	↓14%		↓23%	

45 mg (N = 22)	**Theophylline**		
	400 mg twice daily for 7 days	↑2%	↑5%

* Daily for 7 days unless otherwise noted

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

‡Pioglitazone had no clinically significant effect on prothrombin time

Table 18. Effect of Coadministered Drugs on Pioglitazone Systemic Exposure

Coadministered Drug and Dosage Regimen	**Pioglitazone**		
	Dose Regimen (mg)*	**Change in AUC†**	**Change in Cmax†**
Gemfibrozil 600 mg twice daily for 2 days (N = 12)	15-mg single dose	↑3.2-fold‡	↑6%
Ketoconazole 200 mg twice daily for 7 days (N = 28)	45 mg	↑34%	↑14%
Rifampin 600 mg daily 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%	↑4%
Atorvastatin Ca 80 mg daily for 7 days (N = 24)	45 mg	↓24%	↓31%
Theophylline 400 mg twice daily for 7 days (N = 22)	45 mg	↓4%	↓2%
Topiramate 96 mg twice daily for 7 days§ (N = 26)	30 mg§	↓15%¶	0%

Daily for 7 days unless otherwise noted

†Mean ratio (with/without coadministered drug and no change = 1- fold) % change

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

‡The half- life of pioglitazone increased from 8.3 hours to 22.7 hours in the presence of gemfibrozil

[seeDosage and Administration (2.3) and Drug Interactions (7.1)]

§Indicates duration of concomitant administration with highest twice- daily dose of topiramate from Day 14 onwards over the 22 days of study

¶Additional decrease in active metabolites; 60% for M- III and 16% for M- IV.

Metformin hydrochloride

Effect of Coadministered Drug on Plasma Metformin Systemic Exposure				
	Dose of Coadminist	**Dose of Metfo**		

Coadministered Drug	Drug*		Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.00	
			AUC †	Cmax
No dosing adjustments required for the following:				
Glyburide	5 mg	500 mg§	0.98‡	0.99‡
Furosemide	40 mg	850 mg	1.09‡	1.22‡
Nifedipine	10 mg	850 mg	1.16	1.21
Propranolol	40 mg	850 mg	0.90	0.94
Ibuprofen	400 mg	850 mg	1.05‡	1.07‡
Drugs that are eliminated by renal tubular secretion may increase the accumulation of metformin *[see Warnings and Precautions and Drug Interactions] .*				
Cimetidine	400 mg	850 mg	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis: use with caution *[see Warnings and Precautions and Drug Interactions] .*				
Topiramate	100 mg¶	500 mg¶	1.25¶	1.17

All metformin and coadministered drugs were given as single doses

†AUC = AUC0 to ∞

‡Ratio of arithmetic means

§Metformin hydrochloride extended- release tablets, 500 mg

¶At steady- state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC = AUC0 to 12h

Effect of Metformin on Coadministered Drug Systemic Exposure				
Coadministered Dru	Dose of Coadministe Drug*	Dose of Metformin*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.00	
			AUC †	C_{max}
No dosing adjustments required for the following:				
Glyburide	5 mg	500 mg§	0.98‡	0.99‡
Furosemide	40 mg	850 mg	1.09‡	1.22‡
Nifedipine	10 mg	850 mg	1.16	1.21
Propranolol	40 mg	850 mg	0.90	0.94
Ibuprofen	400 mg	850 mg	1.05‡	1.07‡
Drugs that are eliminated by renal tubular secretion may increase the accumulation of metformin [see Warnings and Precautions and Drug Interactions] .				
Cimetidine	400 mg	850 mg	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis: use with caution *[see Warnings and Precautions and Drug Interactions] .*				
Topiramate	100 mg¶	500 mg¶	1.25¶	1.17

All metformin and coadministered drugs were given as single doses

†AUC = AUC0 to ∞

‡Ratio of arithmetic means

§Metformin hydrochloride extended- release tablets, 500 mg

¶At steady- state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC = AUC0 to 12h

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

*All metformin and coadministered drugs were given as single doses

†AUC = $AUC_{0 \text{ to } \infty}$

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

§AUC reported

¶Ratio of arithmetic means

HOW SUPPLIED/STORAGE AND HANDLING

1-Active ingredients for:

Averofage 15/500 mg F.C.T

Pioglitazone HCl 16.583 mg (eq.to Pioglitazone base 15 mg) + Metformin HCl 500 mg.

Averofage 15/850 mg F.C.T

Pioglitazone HCl 16.583 mg (eq.to Pioglitazone base 15 mg) + Metformin HCl 850 mg

2-Inactive ingredients for:

Averofage 15/500 mg F.C.T

Microcrystalline cellulose – Lactose monohydrate – croscarmellose sodium – sodium lauryl sulfate – Povidone - Maize starch – Magnesium stearate – Hypromellose – PEG 6000 – Talc powder – Titanium dioxide – Polysorbate.

Averofage 15/850 mg F.C.T.

Lactose monohydrate - croscarmellose sodium – Povidone - Magnesium stearate- Hypromellose – PEG 6000 – Talc powder – Titanium dioxide – Polysorbate- Sunset yellow.

3-Pack

Averofage 15/500 mg F.C.T

Carton box contains 1,2 or 3 (Al/white opaque PVC) strips, each of 10 film coated tablets + insert leaflet.

Averofage 15/500 mg F.C.T

Carton box contains 1,2 or 3 (Al/white opaque PVDC) strips, each of 10 film coated tablets + insert leaflet.

4-Shelf life

2 years

PATIENT COUNSELING INFORMATION

- It is important to instruct patients to adhere to dietary instructions and to have blood glucose and glycosylated hemoglobin tested regularly. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be reminded to seek medical advice promptly.
- Tell patients to promptly report any sign of macroscopic hematuria or other symptoms such as dysuria or urinary urgency that develop or increase during treatment as these may be due to bladder cancer.
- Explain to patients the risks of lactic acidosis, its symptoms and conditions that predispose to its development, as noted in the Warnings and Precautions (5.2) section. Advise patients to discontinue pioglitazone and metformin hydrochloride tablets immediately and to promptly notify their healthcare professional if unexplained hyperventilation, myalgia, gastrointestinal symptoms, malaise, unusual somnolence, or other nonspecific symptoms occur. Instruct patients to inform their doctor that they are taking pioglitazone and metformin hydrochloride tablets prior to any surgical or radiological procedure, as temporary discontinuation of pioglitazone and metformin hydrochloride tablets may be required until renal function has been confirmed to be normal.
- Counsel patients against excessive alcohol intake while receiving pioglitazone and metformin hydrochloride tablets.
- Inform patients to immediately report symptoms of an unusually rapid increase in weight or edema, shortness of breath, or other symptoms of heart failure while receiving pioglitazone and metformin hydrochloride tablets.
- Tell patients to promptly stop taking pioglitazone and metformin hydrochloride tablets and seek immediate medical advice if there is unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine as these symptoms may be due to hepatotoxicity.

- Inform patients about the importance of regular testing of renal function and hematologic parameters when receiving treatment with pioglitazone and metformin hydrochloride tablets.
- Inform female patients that treatment with pioglitazone and metformin hydrochloride tablets may result in an unintended pregnancy in some premenopausal anovulatory females due to its effect on ovulation *[see Use in Specific Populations] .*
- Patients should be advised to notify their health practitioner or call the Poison Control Center immediately in case of pioglitazone and metformin hydrochloride tablets overdose.
- Combination antihyperglycemic therapy may cause hypoglycemia. When initiating pioglitazone and metformin hydrochloride tablets, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.
- Patients should be told to take pioglitazone and metformin hydrochloride tablets as prescribed and instructed that any change in dosing should only be done if directed by their physician. If a dose is missed on one day, the dose should not be doubled the following day.

Produced by Averroes Pharma for pharmaceutical industries

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