Bioglita plus
15/500 mg & 15/850 mg film coated tablets
(Pioglitazone and metformin hydrochloride)

WARNING: CONGESTIVE HEART FAILURE AND LACTIC ACIDOSIS

Congestive Heart Failure

- **Thiazolidinediones, including pioglitazone, which is a component of BIOGLITA PLUS, cause or exacerbate congestive heart failure in some patients [see Warnings and Precautions].**
- **After initiation of BIOGLITA PLUS, 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 BIOGLITA PLUS must be considered [see Warnings and Precautions].**
- **BIOGLITA PLUS is not recommended in patients with symptomatic heart failure.**
- **Initiation of BIOGLITA PLUS 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 gapacidosis (without evidence of ketonuria or ketonemia), an increased lactate: pyruvate ratio; and metformin plasma levels generally greater than 5 mcg/mL *[see* Warnings and Precautions (5.2)].**
- **Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast,surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.**
- **Steps to reduce the risk of and manage metformin-associated lactic acidosis inthese high risk groups are provided in the Full Prescribing Information [see Dosage and Administration , Contraindications , Warnings and Precautions , Drug Interactions (7), and Use in Specific Populations].**
- **If metformin-associated lactic acidosis is suspected, immediately discontinue BIOGLITA PLUS and institute general supportive measures in a hospital setting.Prompt hemodialysis is recommended [see Warnings and Precautions].**

1 .INDICATIONS AND USAGE

BIOGLITA PLUS is indicated as an adjunct to diet and exercise to improve glycemic control inadults 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.BIOGLITA PLUS should not be used to treat type 1 diabetes(patients who are taking insulin or nitrates) or diabetic ketoacidosis, as it would not be effective in these settings.

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommendations for All Patients

BIOGLITA PLUS should be taken with meals to reduce the gastrointestinal side effectsassociated with metformin.

If therapy with a combination tablet containing pioglitazone and metformin is consideredappropriate 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, afterassessing 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 responseand tolerability,
- for patients inadequately controlled on pioglitazone monotherapy: 15 mg/500 mg twice dailyor 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 asseparate tablets: BIOGLITA PLUS should be taken at doses that are as close as possibleto the dose of pioglitazone and metformin already being taken.

BIOGLITA PLUS may be titrated up to a maximum daily dose of 45 mg of pioglitazone and2550 mg of metformin.

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

After initiation of BIOGLITA PLUS 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 BIOGLITA PLUS. Routine periodic monitoring of liver tests during treatment with BIOGLITA PLUS is not recommended in patients without liver disease. Patients who have liver test abnormalities prior to initiation of BIOGLITA PLUS or who are found to have abnormal liver tests while taking BIOGLITA PLUS should be managed as described under Warnings and Precautions *[see Warnings and Precautions and Clinical Pharmacology]*.

2.2 Recommendations for Use in Renal Impairment

Assess renal function prior to initiation of BIOGLITA PLUS and periodically thereafter.

BIOGLITA PLUS is contraindicated in patients with an estimated glomerular filtration rate(eGFR) below 30 mL/min/1.73 m^2.

Initiation of BIOGLITA PLUS in patients with an eGFR between 30 – 45 mL/min/1.73 m^2 is not recommended.

In patients taking BIOGLITA PLUS whose eGFR later falls below 45 mL/min/1.73 m^2, assessthe benefit risk of continuing therapy.

Discontinue BIOGLITA PLUS if the patient's eGFR later falls below 30 mL/min/1.73 m^2 *[see Contraindications and Warnings and Precautions].*

2.3 Concomitant Use with Strong CYP2C8 Inhibitors

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

2.4 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue BIOGLITA PLUS at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart BIOGLITA PLUS if renal function is stable *[see Warnings and Precautions].*

3 DOSAGE FORMS AND STRENGTHS

- 15 mg/500 mg film coated tablets are white round biconvex film coated tablets engraved with small letter (a) from one side.
- 15 mg/850 mg film coated tablets are white oblong biconvex film coated tablets

4 CONTRAINDICATIONS

- Initiation in patients with established NYHA Class III or IV heart failure *[see BoxedWarning]*.
- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2) *[see Warnings and Precautions(5.2)]*.
- Use in patients with known hypersensitivity to pioglitazone, metformin, or any othercomponent of BIOGLITA PLUS.
- Metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treatedwith insulin.

5 WARNINGS AND PRECAUTIONS

5.1 Congestive Heart FailurePioglitazone

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 BIOGLITA PLUS 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 BIOGLITA PLUS must be considered *[see Boxed Warning, Contraindications , andAdverse Reactions]*.

Use of pioglitazone is associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction.

5.2 Lactic Acidosis Metformin hydrochloride*Lactic Acidosis*

There have been post-marketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms suchas 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 beinstituted promptly in a hospital setting, along with immediate discontinuation of BIOGLITA PLUS. In pioglitazone and metformin hydrochloride -treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with a clearance of up to 170mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal ofsymptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue BIOGLITA PLUS 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 areprovided below:

Renal Impairment

The post marketing 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 issubstantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include *[see Dosage and Administration , Clinical Pharmacology]*.

- Before initiating BIOGLITA PLUS , obtain an eGFR.
- BIOGLITA PLUS is contraindicated in patients with an eGFR less than 30mL/min /1.73 m^2. Initiation of BIOGLITA PLUS is not recommended in patients with eGFR between 30 – 45 mL/min/1.73 m^2 [*see Contraindications]*.
- Obtain an eGFR at least annually in all patients taking BIOGLITA PLUS . In patients at increased risk for the development of renal impairment (e.g., the elderly), renal functionshould be assessed more frequently.
- In patients taking BIOGLITA PLUS whose eGFR later falls below 45 mL/min/1.73 m^2,assess the benefit and risk of continuing therapy.

Drug Interactions

The concomitant use of BIOGLITA PLUS 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 monitoringof 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 SpecificPopulations]*.

Radiological Studies with Contrast

Administration of intravascular iodinated contrast agents in metformin-treated patients has ledto an acute decrease in renal function and the occurrence of lactic acidosis. Stop BIOGLITA PLUS at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart BIOGLITA PLUS 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. BIOGLITA PLUS should be temporarilydiscontinued while patients have restricted food and fluid intake.

Hypoxic States

Several of the post marketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion andhypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may alsocause prerenal azotemia. When such events occur, discontinue BIOGLITA PLUS .

Excessive Alcohol Intake

Alcohol potentiates the effect of metformin on lactate metabolism and this may increase therisk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intakewhile receiving BIOGLITA PLUS .

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 BIOGLITA PLUS in patients with clinical or laboratory evidence of hepatic disease.

5.3 Edema

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

BIOGLITA PLUS should be used with caution in patients with edema. Because thiazolidinediones, including pioglitazone, can cause fluid retention, which can exacerbate orlead to congestive heart failure, BIOGLITA PLUS should be used with caution in patients at risk for congestive heart failure. Patients treated with BIOGLITA PLUS should be monitored for signs and symptoms of congestive heart failure *[see Boxed Warning, Warnings and Precautions]*.

5.4 Hypoglycemia

Patients receiving BIOGLITA PLUS 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.

5.5 Hepatic Effects

There have been post marketing 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 BIOGLITA PLUS therapy.

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

5.6 Urinary Bladder Tumors

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

Findings regarding the risk of bladder cancer in patients exposed to pioglitazone vary among

observational studies; some did not find an increased risk of bladder cancer associated with pioglitazone, while others did.

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

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

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

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

Counsel patients to report any signs or symptoms of blood in the urine, urinary urgency, pain on urination, or back or abdominal pain, as these may be due to bladder cancer.

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

Encourage patients to read the Medication Guide they get with their pioglitazone medicine.

Report adverse events involving pioglitazone medicines

5.7 Fractures

In PROactive (the Prospective Pioglitazone Clinical Trial in Macrovascular Events), 5238 patients with type 2 diabetes and a history of macrovascular disease were randomized to pioglitazone (N=2605), force-titrated up to 45 mg daily or placebo (N=2633) in addition to standard of care. During a mean follow-up of 34.5 months, the incidence of bone fracture in females was 5.1% (44/870) for pioglitazone versus 2.5% (23/905) for placebo. This differencewas noted after the first year of treatment and persisted during the course of the study. The majority of fractures observed in female patients were non vertebral fractures including lower limb and distal upper limb. No increase in the incidence of fracture was observed in men treated with pioglitazone (1.7%) versus placebo (2.1%). The risk of fracture should be considered in the care of patients, especially female patients, treated with pioglitazone and metformin hydrochloride and attention should be given to assessing and maintaining bone health according to current standards of care.

5.8 Macular Edema

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

Most patients had peripheral edema at the time macular edema was diagnosed. Some patientshad 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 orother physical findings *[see*

Adverse Reactions].

5.9 Vitamin B_{12} Levels

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

5.10 Macrovascular Outcomes

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

6 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]

6.1 Clinical Trials Experience

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

Pioglitazone

The most common adverse events leading to withdrawal were related to inadequate glycemic control, although

the incidence of these events was lower (1.5%) with pioglitazone than with placebo (3.0%).

Congestive heart failure was the most common serious adverse event leading to withdrawal occurring in 1.3% of patients treated with pioglitazone and 0.6% of patients treated with placebo.

- **Adverse reactions in Patients Treated with Pioglitazone monotheraoy :**

  Upper Respiratory Tract Infection, Headache,Sinusitis ,Myalgia ,Pharyngitis

- **Adverse reactions in Patients Treated with Pioglitazone + Metformin**

  Edema,Headache, Upper Respiratory Tract Infection,Weight Increased

- **Adverse reactions in Patients with Inadequate Glycemic Control on Diet and Exercise**

  Diarrhea, Headache

- **PROactive trial : Adverse reactions in Patients Treated with Pioglitazone**

  Hypoglycemia, Edema,Cardiac Failure,Pain in Extremity,Back Pain &Chest Pain

Congestive Heart Failure

A summary of the incidence of adverse events related to congestive heart failure is provided inTable 5 for the 16- to 24-week add-on to metformin trials. None of the events were fatal.

Table 1. Treatment-Emergent Adverse Events of Congestive Heart Failure (CHF) Patients Treated with Pioglitazone or Placebo Added on to Metformin

	Number (%) of Patients			
	Placebo-Controlled Trial(16 weeks)		**Non-Controlled Double-Blind Trial(24 weeks)**	
	Placebo + Metformin N=160	**Pioglitazone 30 mg + Metformin** N=168	**Pioglitazone 30 mg + Metformin** N=411	**Pioglitazone 45 mg + Metformin** N=416
At least one congestive heart failure event	0	1 (0.6%)	0	1 (0.2%)
Hospitalized	0	1 (0.6%)	0	1 (0.2%)

Table 2. Treatment-Emergent Adverse Events of Congestive Heart Failure (CHF)

Patients Treated with Pioglitazone or Placebo Added on to a Sulfonylurea

	Number (%) of Patients				
	Placebo-Controlled Trial(16 weeks)			**Non-Controlled Double-Blind Trial(24 weeks)**	
	Placebo + Sulfonylurea N=187	**Pioglitazone15 mg + Sulfonylurea** N=184	**Pioglitazone30 mg + Sulfonylurea** N=189	**Pioglitazone30 mg + Sulfonylurea** N=351	**Pioglitazone45 mg + Sulfonylurea** N=351
At least one congestive heart failure event	2 (1.1%)	0	0	1 (0.3%)	6 (1.7%)

Hospitalized	2 (1.1%)	0	0	0	2 (0.6%)
Patients Treated with Pioglitazone or Placebo Added on to Insulin					
	Number (%) of Patients				
	Placebo-Controlled Trial(16 weeks)			**Non-Controlled Double-Blind Trial(24 weeks)**	
	Placebo + Insulin N=187	**Pioglitazone15 mg + Insulin** N=191	**Pioglitazone30 mg + Insulin** N=188	**Pioglitazone30 mg + Insulin** N=345	**Pioglitazone45 mg + Insulin** N=345
At least one congestive heartfailure event	0	2 (1.0%)	2 (1.1%)	3 (0.9%)	5 (1.4%)
Hospitalized	0	2 (1.0%)	1 (0.5%)	1 (0.3%)	3 (0.9%)
Patients Treated with Pioglitazone or Placebo Added on to Metformin					
	Number (%) of Patients				
	Placebo-Controlled Trial(16 weeks)		**Non-Controlled Double-Blind Trial(24 weeks)**		
	Placebo + Metformin N=160	**Pioglitazone30 mg + Metformin** N=168	**Pioglitazone30 mg + Metformin** N=411	**Pioglitazone45 mg + Metformin** N=416	
At least one congestive heartfailure event	0	1 (0.6%)	0	1 (0.2%)	
Hospitalized	0	1 (0.6%)	0	1 (0.2%)	

Table 3. Treatment-Emergent Adverse Events of Congestive Heart Failure (CHF) in Patients with NYHA Class II or III Congestive Heart FailureTreated 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 worseningCHF (adjudicated)	26 (9.9%)	12 (4.7%)
Emergency room visit for CHF (adjudicated)	4 (1.5%)	3 (1.2%)
Patients experiencing CHF progression during study	35 (13.4%)	21 (8.2%)

Congestive heart failure events leading to hospitalization that occurred during the PROactivetrial are summarized in Table 4.

Table 4. Treatment-Emergent Adverse Events of Congestive Heart Failure (CHF)in PROactive Trial

	Number (%) of Patients	
	Placebo N=2633	**Pioglitazone** N=2605
At least one hospitalized congestive heart failure event	108 (4.1%)	149 (5.7%)
Fatal	22 (0.8%)	25 (1.0%)
Hospitalized, nonfatal	86 (3.3%)	124 (4.7%)

Cardiovascular Safety

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

The primary objective of this trial was to examine the effect of pioglitazone on mortality and macrovascular morbidity in patients with type 2 diabetes mellitus who were at high risk for macrovascular events. The primary efficacy variable was the time to the first occurrence of anyevent in a cardiovascular composite endpoint that included all-cause mortality, nonfatal myocardial infarction (MI) including silent MI, stroke, acute coronary syndrome, cardiac intervention including coronary

artery bypass grafting or percutaneous intervention, major leg amputation above the ankle, and bypass surgery or revascularization in the leg. A total of 514 (19.7%) patients treated with pioglitazone and 572 (21.7%) placebo-treated patients experienced at least one event from the primary composite endpoint (HR 0.90; 95% CI: 0.80,1.02; p=0.10).

Although there was no statistically significant difference between pioglitazone and placebo forthe three-year incidence of a first event within this composite, there was no increase in mortality or in total macrovascular events with pioglitazone. The number of first occurrences and total individual events contributing to the primary composite endpoint is shown in Table 9.

Table 5. PROactive Trial: Number of First and Total Events for Each Component Within the Cardiovascular Composite Endpoint

	Placebo N=2633		**Pioglitazone** N=2605	
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

CABG = coronary artery bypass grafting; PCI = percutaneous intervention

Weight Gain

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

Edema

Edema induced from taking pioglitazone is reversible when pioglitazone is discontinued. Theedema

usually does not require hospitalization unless there is coexisting congestive heart failure.

Hepatic Effects

There has been no evidence of pioglitazone-induced hepatotoxicity in the pioglitazone controlled clinical trial database to date. One randomized, double-blind, three-year trial comparing pioglitazone to glyburide as add-on to metformin and insulin therapy was specifically designed to evaluate the incidence of serum ALT elevation to greater than three times the upper limit of the reference range, measured every eight weeks for the first 48 weeks of the trial then every 12 weeks thereafter. A total of 3/1051 (0.3%) patients treated with pioglitazone and 9/1046 (0.9%) patients treated with glyburide developed ALT values greater than three times the upper limit of the reference range. None of the patients treated with pioglitazone in the pioglitazone controlled clinical trial database to date have had a serum ALT greater than three times the upper limit of the reference range and a corresponding total bilirubin greater than two times the upper limit of the reference range, a combination predictiveof the potential for severe drug-induced liver injury.

Hypoglycemia

In the pioglitazone clinical trials, adverse events of hypoglycemia were reported based on clinical judgment of the investigators and did not require confirmation with finger stick glucose testing. In the 16-week add-on to sulfonylurea trial, the incidence of reported hypoglycemia was 3.7% with pioglitazone 30 mg and 0.5% with placebo. In the 16-week add-on to insulin trial, the incidence of reported hypoglycemia was 7.9% with pioglitazone 15 mg, 15.4% with pioglitazone 30 mg, and 4.8% with placebo.

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

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

Urinary Bladder Tumors

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

Metformin hydrochloride

Adverse reactions reported in greater than 5% of the metformin patients, and that were more common

in metformin than placebo-treated patients, are listed in Table 15. In this trial, diarrhea led to discontinuation of study medication in 6% of patients treated with metformin.

Most Common Adverse Reactions in a Placebo-Controlled Clinical Study of Metformin Monotherapy:

Diarrhea ,Nausea/Vomiting ,Flatulence ,Asthenia ,Indigestion ,Abdominal Discomfort &Headache

Laboratory Abnormalities Hematologic Effects

Hematologic Effects

Pioglitazone may cause decreases in hemoglobin and hematocrit. In placebo-controlled monotherapy trials, mean hemoglobin values declined by 2% to 4% in patients treated with pioglitazone compared with a mean change in hemoglobin of -1% to +1% in placebo-treated patients. These changes primarily occurred within the first four to 12 weeks of therapy and remained relatively constant thereafter. These changes may be related to increased plasma volume associated with pioglitazone therapy and are not likely to be associated with any clinically significant hematologic effects.

Vitamin B_{12} Concentrations

Metformin may lower serum vitamin B_{12} concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on BIOGLITA PLUS and any apparentabnormalities 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.

6.2 Postmarketing Experience

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

Pioglitazone

- New onset or worsening diabetic macular edema with decreased visual acuity
- Fatal and nonfatal hepatic failure

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 asexcessive edema and

congestive heart failurefailure [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 authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. You can report side effects at Al Andalous website: (www.alandalous.org) or (Pv@alandalous.org) or pv.report@edaegypt.gov.eg

7 DRUG INTERACTIONS

7.1 Strong CYP2C8 Inhibitors

An inhibitor of CYP2C8 (e.g., gemfibrozil) significantly increases the exposure (area under theserum concentration-time curve or AUC) and half-life ($t_{1/2}$) of pioglitazone. Therefore, the maximum recommended dose of pioglitazone is 15 mg daily if used in combination with gemfibrozil or other strong CYP2C8 inhibitors *[see Dosage and Administration and Clinical Pharmacology]*.

7.2 CYP2C8 Inducers

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

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 withBIOGLITA PLUS 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 involvedin 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]*. 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 BIOGLITA PLUS .Insulin Secretagogues or Insulin If hypoglycemia occurs in a patient coadministered BIOGLITA PLUS and an insulin secretagogue (e.g., sulfonylurea), the dose of the insulin secretagogue should be reduced.

If hypoglycemia occurs in a patient coadministered BIOGLITA PLUS and insulin, the

dose of insulin should be decreased by 10% to 25%. Further adjustments to the insulin doseshould be individualized based on glycemic response.

7.6 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 BIOGLITA PLUS , the patient should be closely observed for loss of blood glucose control.

When such drugs are withdrawn from a patient receiving BIOGLITA PLUS , the patient should be observed closely for hypoglycemia.

7.7 Topiramate

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited data with pioglitazone and metformin hydrochloride or pioglitazone in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. Published studies withmetformin 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 *[see Clinical Considerations]*.

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

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

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

Data

Human Data

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

Pioglitazone

Pioglitazone administered to pregnant rats during organogenesis did not cause adverse developmental effects at a dose of 20 mg/kg (~5-times the 45 mg clinical dose), but delayed parturition and reduced

embryofetal viability at 40 and 80 mg/kg, or ≥9-times the 45 mg clinicaldose, by body surface area. In pregnant rabbits administered pioglitazone during organogenesis, no adverse developmental effects were observed at 80 mg/kg (~35-times the 45 mg clinical dose), but reduced embryofetal viability at 160 mg/kg, or ~69-times the 45 mg clinical dose, by body surface area. When pregnant rats received pioglitazone during late gestation and lactation, delayed postnatal development, attributed to decreased body weight, occurred in offspring at maternal doses of 10 mg/kg and above or ≥2-times the 45 mg clinical dose, by body surface area.

Metformin hydrochloride

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

8.2 Lactation

Risk Summary

There is no information regarding the presence of pioglitazone and metformin hydrochloride or pioglitazone in human milk, the effects on the breastfed infant, or the effects on milk production. Pioglitazone is present in rat milk; however, due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk. Limited published studies report that metformin is present in human milk *[see Data]*. However, there is insufficient information on theeffects 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 BIOGLITA PLUS and any potential adverse effects on the breastfed infant from BIOGLITA PLUS 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 designedto 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 /metformin hydrochloride, may result in ovulation in some anovulatory women.

8.4 Pediatric Use

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

BIOGLITA PLUS is not recommended for use in pediatric patients based on adverse effects observed in adults, including fluid retention and congestive heart failure, fractures, and urinarybladder tumors *[see Warnings and Precautions]*.

8.5 Geriatric

UsePioglitazone

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 atthe 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].*

8.6 Renal Impairment

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation andlactic acidosis increases with the degree of renal impairment. BIOGLITA PLUS is contraindicated in severe renal impairment, patients with an eGFR below 30 mL/min/1.73 m^2 *[see Dosage and Administration , Contraindications , Warnings and Precautions and Clinical Pharmacology].*

8.7 Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases oflactic acidosis. BIOGLITA PLUS is not recommended in patients with hepatic impairment *[seeWarnings and Precautions]*.

10 OVERDOSAGE

Pioglitazone

During controlled clinical trials, one case of overdose with pioglitazone was reported. A male patient took 120 mg per day for four days, then 180 mg per day for seven days. The patient denied any clinical symptoms during this period. In the event of overdosage, appropriate supportive treatment should be initiated according tothe 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 hemodynamicconditions. Therefore, hemodialysis may be useful for removal of accumulated metformin from patients in whom metformin overdosage is suspected.

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

BIOGLITA PLUS combines two antidiabetic medications with different mechanisms of action to

improve glycemic control in adults with type 2 diabetes: pioglitazone, a thiazolidinedione, and metformin hydrochloride, a biguanide. Thiazolidinediones are insulin-sensitizing agents that act primarily by enhancing peripheral glucose utilization, whereas biguanides act primarilyby decreasing endogenous hepatic glucose production.

Pioglitazone

Pioglitazone is a thiazolidinedione that depends on the presence of insulin for its mechanism ofaction. 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 genesinvolved 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.

11.2 Pharmacodynamics

Pioglitazone

Clinical studies demonstrate that pioglitazone improves insulin sensitivity in insulin-resistant patients. Pioglitazone enhances cellular responsiveness to insulin, increases insulin- dependent glucose disposal and improves hepatic sensitivity to insulin. In patients with type 2diabetes, 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 *[see Warnings and Precautions and Adverse Reactions]*.

In a 26-week, placebo-controlled, dose-ranging monotherapy study, mean serum triglycerides

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

Table . Lipids in a 26-Week Placebo-Controlled Monotherapy Dose-Ranging Study				
	Placebo	**Pioglitazone 15 mg Once Daily**	**Pioglitazone 30 mg Once Daily**	**Pioglitazone 45 mg Once Daily**
Triglycerides (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	263	284	261	260
Percent change from baseline (adjusted mean*)	4.8%	-9.0%†	-9.6%†	-9.3%†
HDL Cholesterol (mg/dL)	N=79	N=79	N=83	N=77
Baseline (mean)	42	40	41	41
Percent change from baseline (adjusted mean*)	8.1%	14.1%†	12.2%	19.1%†
LDL Cholesterol (mg/dL)	N=65	N=63	N=74	N=62
Baseline (mean)	139	132	136	127
Percent change from baseline (adjusted mean*)	4.8%	7.2%	5.2%	6.0%
Total Cholesterol (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	225	220	223	214
Percent change from baseline (adjusted mean*)	4.4%	4.6%	3.3%	6.4%

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

†$p < 0.05$ versus placebo

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

11.3 Pharmacokinetics

Absorption

BIOGLITA PLUS

In bioequivalence studies of Pioglitazone /metformin hydrochloride 15 mg/500 mg and 15 mg/850 mg,

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

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

Pioglitazone

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

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

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

Metformin hydrochloride

The absolute bioavailability of a 500 mg metformin tablet given under fasting conditions is approximately 50% - 60%. Studies using single oral doses of metformin tablets of 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.At usual clinical doses and dosing schedules of metformin, steady-state plasma concentrationsof 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 meanC_{max}, a 25% lower AUC, and a 35-minute prolongation of T_{max} following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Pioglitazone

The mean apparent volume of distribution (Vd/F) of pioglitazone following single-dose administration is 0.63 ± 0.41 (mean ± SD) L/kg of body weight. Pioglitazone is extensively protein bound (>99%) in

human serum, principally to serum albumin. Pioglitazone also binds toother 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 alsopartly convert to glucuronide or sulfate conjugates. Metabolites M-III and M-IV are the majorcirculating 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, showedthat pioglitazone is a CYP2C8 substrate *[see Dosage and Administration (2.3) and Drug Interactions (7.1)]*. Urinary 6ß-hydroxycortisol/cortisol ratios measured in patients treated withpioglitazone 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 beenidentified in humans) nor biliary excretion.

Excretion and Elimination

Pioglitazone

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

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

Metformin hydrochloride

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

a plasma elimination $t_{1/2}$ of approximately 6.2 hours. In blood, the elimination $t_{1/2}$ is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Specific Populations

Renal Impairment

Pioglitazone

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

Metformin hydrochloride

In patients with decreased renal function, the plasma and blood $t_{1/2}$ of metformin is prolonged and the renal clearance is decreased *[see Dosage and Administration , Contraindications and Warnings and Precautions]*.

Hepatic Impairment

Pioglitazone

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

There are postmarketing reports of liver failure with pioglitazone and clinical trials have generally excluded patients with serum ALT >2.5 times the upper limit of the reference range.Use BIOGLITA PLUS 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, C_{max} of pioglitazone was not significantly different, but AUC valueswere approximately 21% higher than those achieved in younger subjects. The mean $t_{1/2}$ of pioglitazone was also prolonged in elderly subjects (about ten hours) as compared to youngersubjects (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 $t_{1/2}$ is prolonged, and C_{max} is increased, compared tohealthy 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. BIOGLITA PLUS is 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 C_{max} and AUC differed less than 5% between pediatric type 2 diabetic patients (12to 16 years of age) and gender- and weight-matched healthy adults (20 to 45 years of age), and all with normal renal function.

***Gende*r**

Pioglitazone

The mean C_{max} and AUC values of pioglitazone were increased 20% to 60% in women compared to men. In controlled clinical trials, HbA1c decreases from baseline were generally greater for females than for males (average mean difference in HbA1c 0.5%). Because therapyshould 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 antihyperglycemiceffect 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 BIOGLITA PLUS 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	**Name and Dose Regimens**	**Chang ein**	**Chang ein**

Regimen (mg)*		AUC†		C_{max}†	
45 mg (N = 12)	**Warfarin‡**				
	Daily loading then maintenance dosesbased 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 increaseand decrease, respectively

‡Pioglitazone had no clinically significant effect on prothrombin time

Table . Effect of Coadministered Drugs on Pioglitazone Systemic Exposure

Coadministered Drug andDosage Regimen	**Pioglitazone**		
	Dose Regimen (mg)*	**Changein AUC†**	**Changein C_{max}†**
Gemfibrozil 600 mg twice daily for 2 days(N = 12)	15-mg single dose	↑3.2-fold‡	↑6%
Ketoconazole 200 mgtwice daily for 7 days (N = 28)	45 mg	↑34%	↑14%
Rifampin 600 mgdaily for 5 days (N = 10)	30-mg single dose	↓54%	↓5%
Fexofenadine 60 mgtwice 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 mgdaily for 7 days (N = 23)	45 mg	↑5%	↑4%
Atorvastatin Ca 80 mgdaily for 7 days (N = 24)	45 mg	↓24%	↓31%
Theophylline 400 mgtwice 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/withoutcoadministered 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 ofgemfibrozil *[see Dosage and Administration (2.3) and Drug Interactions (7.1)]*

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

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

Metformin hydrochloride

Table . Effect of Coadministered Drug on Plasma Metformin Systemic Exposure				
CoadministeredDrug	**Dose of Coadministered Drug***	**Dose of Metformin***	**Geometric Mean Ratio(ratio with/without coadministered drug)** No effect = 1.00	
			AUC†	**C_{max}**
No dosing adjustments required for the following:				
Glyburide	5 mg	500 mg§	0.98‡	0.99‡
Furosemide	40 mg	850 mg	1.09‡	1.22‡
Nifedipine	10 mg	850 mg	1.16	1.21
Propranolol	40 mg	850 mg	0.90	0.94
Ibuprofen	400 mg	850 mg	1.05‡	1.07‡
Drugs that are eliminated by renal tubular secretion may increase the accumulation of metformin *[see Warnings and Precautions (5) and Drug Interactions (7)]*.				
Cimetidine	400 mg	850 mg	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis *[see Warnings and Precautions (5) and Drug Interactions (7)]*.				
Topiramate	100 mg¶	500 mg¶	1.25¶	1.17

*All metformin and coadministered drugs were given as single doses

†AUC = $AUC_{0-\infty}$

‡Ratio of arithmetic means

§Metformin hydrochloride extended-release tablets, 500 mg

¶At steady-state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC = AUC_{0-12h}

Table. 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†	Cmax
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 = $AUC_{0-\infty}$

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

§AUC_{0-24hr} reported

¶Ratio of arithmetic means

12 HOW SUPPLIED/STORAGE AND HANDLING

12.1: Pack: carton box containing 1 or 2 or 3 (AL/AL) strips, each of 10 film coated tablets and an inner leaflet.

12.2: Storage: Store at temperature not exceeding 25°C.

12.3 shelf life: 2 years

12.4: **Composition:**

Each film coated tablet contains:

For Bioglita Plus 15/500mg:

Active Ingredients: pioglitazone HCl 16.5 mg Eq.To 15 mg pioglitazone and Metformin hydrochloride 500 mg

Inactive Ingredients: povidone K30, magnesium stearate, croscarmellose sodium, aerosil 200, microcrystalline cellulose PH101

Film coat: hydroxyl propyl methyl celluloseE5, titanium dioxide, polyethylene glycol 6000, purified talc

For Bioglita Plus 15/850mg:

Active Ingredients: pioglitazone HCl 16.5 mg Eq.To 15 mg pioglitazone, Metformin hydrochloride 850 mg

Inative Ingredients: povidone K30, magnesium stearate, croscarmellose sodium, aerosil 200, microcrystalline cellulosePH101.

Film coat: hydroxyl propyl methyl cellulose, titanium dioxide, polyethylene glycol 6000, purified talc

Manufacturer name & license holder: Al Andalous for Pharmaceutical Industries