SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Bioglita Plus 15/850mg film coated tablets

2. Qualitative and quantitative composition

Active Ingredients: Pioglitazone HCl Eq. To 15 mg pioglitazone, Metformin hydrochloride
Inactive Ingredients: Microcrystalline cellulose PH 101, Croscarmellose sodium, Povidone K30, Magnesium stearate, Hydroxyl propyl methyl cellulose E5, Polyethylene glycol 6000, Titanium dioxide (C.I.No.77891), Talc.

3. Pharmaceutical form

Film Coated Tablets

4. Clinical particulars

4.1 Therapeutic indications

Bioglita Plus is 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. Bioglita plus should not be used to treat type 1 diabetes or diabetic ketoacidosis, as it would not be effective in these settings.

Use caution in patients with liver disease [*see Warnings and Precautions (5.5)*].

4.2 Posology and method of administration

1. Recommendations for All Patients

Bioglita plus 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: Bioglita should be taken at doses that are as close as possible to 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 and 2550 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 (5.1)]. 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
[s*ee Warnings and Precautions (5.5) and Clinical Pharmacology (12.3)*].

2. Concomitant Use with an Insulin Secretagogue 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 dose should be individualized based on glycemic response.

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 *(7.1) and Clinical Pharmacology (12.3)*].

4.3 Contraindications

* Initiation in patients with established NYHA Class III or IV heart failure [*see Boxed Warning*].
* Renal impairment (e.g., serum creatinine levels =1.5 mg/dL [males], =1.4 mg/dL [females], or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia [*see Warnings and Precautions (5.2, 5.10)*].
* Use in patients with known hypersensitivity to pioglitazone, metformin, or any other component of Bioglita Plus.
* Metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.

4.4 Special warnings and precautions for use

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 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 BioglitaPlus must be considered [*see Boxed Warning, Contraindications (4), and Adverse Reactions (6.1)*].

2. **Lactic Acidosis**

Metformin hydrochloride

Lactic Acidosis

Lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during treatment with Bioglita plus and it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate concentrations (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 mcg/mL are generally found. Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, particularly when accompanied byhypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Bioglita Plus treatment should not be initiated in any patient unless measurement of creatinine clearance demonstrates that renal function is not reduced. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic impairment.

Patients should be cautioned against excessive alcohol intake when taking metformin, because alcohol potentiates the effects of metformin on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure necessitating restricted intake of food or fluids. Use of topiramate, a carbonic anhydrase inhibitor, in epilepsy and migraine prophylaxis may frequently cause dose-dependent metabolic acidosis and may exacerbate the risk of metformin-induced lactic acidosis.

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

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be

explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.
Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).
Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery.

3. Edema

Bioglita Plus 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, 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 .

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 Dosage and Administration (2.2)*]. Hypoglycemia can also occur when caloric intake is deficient or when strenuous exercise is not compensated by caloric supplement. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

5. Hepatic Effects

There have been postmarketing reports of fatal and nonfatal hepatic failure in patients taking pioglitazone, although the reports contain insufficient information necessary to establish the probable cause. There has been no evidence of drug-induced hepatotoxicity in the pioglitazone controlled clinical trial database to date [see Adverse Reactions (6.1)]. Patients with type 2 diabetes may have fatty liver disease or cardiac disease with episodic congestive heart failure, both of whichmay 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 patients with lesser elevations

of serum ALT or bilirubin and with an alternate probable cause, treatment with Bioglita plus can be used with caution. Because impaired hepatic function has been associated with some cases of lactic acidosis Bioglita plus should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

6. Urinary Bladder Tumors

There are insufficient data to determine whether pioglitazone is a tumor promoter for urinary bladder tumors. 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.

7. Fractures

The risk of fracture should be considered in the care of patients, especially female patients, treated with Bioglita plus 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 (6.1)].

9. Ovulation

Therapy with pioglitazone, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking Bioglita plus [*see Use in Specific Populations (8.1)*].

This effect has not been investigated in clinical trials, so the frequency of this occurrence is not known. Adequate contraception in all premenopausal women treated with Bioglita plus is recommended.

10. Monitoring of Renal Function

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

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

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

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

Radiological Studies and Surgical Procedures

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT)

scans with intravascular contrast materials) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin [see Contraindications (4)]. Therefore, in patients in whom any such study is planned, Bioglita plus should be discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

11. Hypoxic States

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

12. Surgical Procedures

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

13. Alcohol Intake

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

14. Vitamin B12 Levels

In controlled clinical trials of metformin of 29 weeks' duration, 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 Bioglita plus 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.

15. Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Bioglita plus or any other oral antidiabetic drug.

4.5 Interaction with other medicinal products and other forms of interaction

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 inhibitor.

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 .

3. Carbonic Anhydrase Inhibitors

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

4. Cationic Drugs

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

5. Drugs Affecting Glycemic Control

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

4.6 Fertility, pregnancy and lactation

1. Pregnancy Category C

Bioglita plus should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pioglitazone

Clinical Considerations

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

Metformin hydrochloride

Metformin was not teratogenic in rats and rabbits at doses up to 600mg/kg/day. However, because animal reproduction studies are not always predictive of human response, metformin should not be used during pregnancy unless clearly needed.

2. Labor and Delivery

The effect of Bioglita plus on labor and delivery in humans is not known.

3. Nursing Mothers

Because many drugs are excreted in human milk, and because of the potential for Bioglita plus to cause serious adverse reactions in nursing infants, a decision should be made to discontinue nursing or discontinue Bioglita plus, taking into account the importance of Bioglita plus to the mother.

4. Pediatric Use

Safety and effectiveness of Bioglita plus 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 urinary bladder tumors .

5. Geriatric Use

Pioglitazone

In pharmacokinetic studies with pioglitazone, no significant differences were observed in pharmacokinetic parameters between elderly and younger patients.

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.

Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, Bioglita plus should only be used in patients with normal renal function. Because aging is associated with reduced renal function, Bioglita plus should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function.

Generally, elderly patients should not be titrated to the maximum dose of Bioglita plus[*see Warnings and Precautions and Dosage and Administration* .

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

ADVERSE REACTIONS

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

*Congestive heart failure [*see Boxed Warning and Warnings and Precautions (5.1)*]

*Lactic acidosis [*see Boxed Warning and Warnings and Precautions (5.2)*]

*Edema [*see Warnings and Precautions (5.3)*]

*Fractures [*see Warnings and Precautions (5.7)*]

Pioglitazone

- Adverse reactions in Patients Treated with Pioglitazone monotherapy:

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

- Adverse reactions in Patients Treated with Pioglitazone: PROactive trial

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

TreatmentEmergent Adverse Events of Congestive Heart Failure (CHF) in Patients with NYHA Class II or III Congestive Heart Failure Treated with Pioglitazone or Glyburide		
	Number (%) of Subjects	
	Pioglitazone N=262	Glyburide N=256
Death due to cardiovascular causes (adjudicated)	5 (1.9%)	6 (2.3%)
Overnight hospitalization for worsening CHF (adjudicated)	26 (9.9%)	12 (4.7%)
Emergency room visit for CHF (adjudicated)	4 (1.5%)	3 (1.2%)
Patients experiencing CHF progression during study	35 (13.4%)	21 (8.2%)

Cardiovascular Events

Nonfatal myocardial infarction (MI), Stroke, Acute coronary syndrome, Cardiac intervention (CABG/PCI), Major leg amputation, Leg revascularization

Cardiovascular Events

Nonfatal myocardial infarction (MI)
Stroke
Acute coronary syndrome
Cardiac intervention (CABG/PCI)
Major leg amputation
Leg revascularization

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. The edema 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.

None of the patients treated with pioglitazone in the pioglitazone controlled clinical trial database to date have had a serum ALT greater than three times the upper limit of the reference range and a corresponding total bilirubin greater than two times the upper limit of the reference range, a combination predictive of the potential for severe drug-induced liver injury.

Hypoglycemia

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

Urinary Bladder Tumors

Tumors were observed in the urinary bladder of male rats in the two-year carcinogenicity study. There are too few events of bladder cancer to establish causality.\

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 below. In this trial, diarrhea led to discontinuation of study medication in 6% of patients treated with metformin.

Adverse Reaction

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

Laboratory Abnormalities Hematologic Effects
Pioglitazone may cause decreases in hemoglobin and hematocrit.
Vitamin B12 Concentrations
Metformin may lower serum vitamin B12 concentrations. 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.
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 and in no comparator-treated patients.
The relationship of these events to pioglitazone therapy is unknown.

4.9 Overdose
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. 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.

5. Pharmacological properties

5.1 Pharmacodynamics:
Pioglitazone
Clinical studies demonstrate that pioglitazone improves insulin sensitivity in insulin-resistant patients. Pioglitazone enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal and improves hepatic sensitivity to insulin. In patients with type 2 diabetes, the decreased insulin resistance produced by pioglitazone results in lower plasma glucose concentrations, lower plasma insulin concentrations, and lower HbA1c values. In controlled clinical trials, pioglitazone had an additive effect on glycemic control when used in combination with a sulfonylurea, metformin, or insulin.
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 There were no consistent differences for LDL and total cholesterol in patients treated with pioglitazone compared to placebo.

5.2 Pharmacokinetics

Bioglita plus

Administration of Bioglita 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 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 (Cmin) 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, Tmax 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% -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 Tmax 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. 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 (based on CLcr), the plasma and blood t1/2 of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in CLcr. Because metformin is contraindicated in patients with renal impairment, Bioglita plus is also contraindicated in these patients.

Hepatic Impairment

Pioglitazone

Compared with healthy controls, subjects with impaired hepatic function (Child-Turcotte-Pugh Grade B/C) have an approximate 45% reduction in pioglitazone and total pioglitazone (pioglitazone, M-III, and M-IV) mean 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 Bioglita plus with caution in patients with liver disease.

Metformin hydrochloride

No pharmacokinetic studies of metformin have been conducted in subjects with hepatic impairment. Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Bioglita plus is not recommended in patients with hepatic impairment [see Warnings and Precautions (5.5)].

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.

As is true for all patients, Bioglita plus treatment should not be initiated in geriatric patients unless measurement of CLcr demonstrates that renal function is not reduced Pediatrics

Pioglitazone

Safety and efficacy of pioglitazone in pediatric patients have not been established. Bioglita plus is not recommended for use in pediatric patients.

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. 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.

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

Pioglitazone Dosage Regimen (mg)*	Coadministered Drug: Name and Dose Regimens	Change in AUC†		Change in Cmax †	
45 mg (N = 12)	**Warfarin‡**	R-Warfarin	↓3%	R-Warfarin	↓2%
	Daily loading then maintenance doses based PT and INR values Quick's Value = 35 ± 5%	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 for 5 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%

*Daily for 7 days unless otherwise noted
†Mean ratio (with/without coadministered drug and no change = 1-fold) % change (with/without coadministered drug and no change = 0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively
‡The half-life of pioglitazone increased from 8.3 hours to 22.7 hours in the presence of gemfibrozil [see Dosage and Administration and Drug Interactions]
Metformin hydrochloride

Table 19. Effect of Coadministered Drug on Plasma Metformin 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§	0.98‡	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‡
Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination: use with caution *[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 = AUC0–8
‡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 = AUC0-12h

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†	**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 = AUC0–8
‡Ratio of arithmetic means, p-value of difference <0.05 §AUC0-24hr reported Ratio of arithmetic means

5.3 Preclinical safety data
None.

6. Pharmaceutical particulars
6.1 List of excipients
Microcrystalline cellulose PH 101, Croscarmellose sodium, Povidone K30, Magnesium stearate, Hydroxyl propyl methyl cellulose E5, Polyethylene glycol 6000, Titanium dioxide, Talc.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Store at temperature not exceeding 25º C.
Keep all medicines out of reach of children.

6.5 Nature and contents of container
Carton box containing 1, 2 or 3 (Al/Al) strips, each of 10 tablets + inner leaflet.

6.6 Special precautions for disposal and other handling
None.

7. Marketing authorisation holder
Al Andalous for pharmaceutical industries

8. Marketing authorisation number(s)
25602/2008

9. Date of first authorisation/renewal of the authorisation
28/08/2008

10. Date of revision of the text
12/2021