For the Use of a Registered Medical Practitioner Only

Advice for healthcare professionals

- Patients with active bladder cancer or with a history of bladder cancer, and those with uninvestigated haematuria, should not receive pioglitazone.
- Prescribers should review the safety and efficacy of pioglitazone in individuals after 3-6 months of treatment to ensure that only patients who are deriving benefit continue to be treated. Pioglitazone should be stopped in patients who do not respond adequately to treatment (eg, reduction in glycosylated haemoglobin HbA1c).
- Before starting pioglitazone, the following known risk factors for development of bladder cancer should be assessed in individuals: age, current or past history of smoking, exposure to some occupational or chemotherapy agents such as cyclophosphamide, or previous irradiation of the pelvic region.
- Use in elderly patients should be considered carefully before and during treatment because the risk of bladder cancer increases with age. Elderly patients should start on the lowest possible dose, and be regularly monitored because of the risks of bladder cancer and heart failure associated with pioglitazone.

1. GENERIC NAME & BRAND NAMR

Pioglitazone, Glimepiride and Extended Release Metformin Hydrochloride Tablets

Tribet® 1 / 2

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tribet® 1

Each uncoated bilayered tablet contains:

Pioglitazone Hydrochloride I.P.	
Equivalent to Pioglitazone	15 mg
Glimepiride I.P.	1 mg
Metformin Hydrochloride I.P. (as extended release)	500mg
Excipients	q.s.
Colour: Lake of Erythrosine	

Tribet® 2

Each uncoated bilayered tablet contains:

Pioglitazone Hydrochloride I.P.	
Equivalent to Pioglitazone	15 mg
Glimepiride I.P.	2 mg
Metformin Hydrochloride I.P. (as extended release)	500mg
Excipients	q.s.
Colour: Brilliant Blue FCF	

3. DOSAGE FORM AND STRENGTH

Kindly refer section 1 & 2

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATION

Treatment of type-2 diabetes mellitus (T2DM) when diet, exercise along with monotherapy and dual therapy does not achieve glycaemic target.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

3 tablets per day orally, as a single dose, or as directed by the physician.

4.3 CONTRAINDICATIONS

- TRIBET is contraindicated in patients with a history of a hypersensitivity reactions/ allergic reactions to Glimepiride and/ or Metformin or Pioglitazone
- TRIBET is contraindicated in patients with type 1 diabetes since Glimepiride requires the presence of functioning beta cells in the pancreas
- Metformin hydrochloride is contraindicated in patients with renal disease (serum creatininelevels ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females] or abnormal creatinine clearance).
- Moderate stage 3b and severe renal failure or renal dysfunction (CrCL<45ml/min or eGFR<45 ml/min/1.73m^2
- Acute conditions with the potential to alter renal function such as dehydration ,severe infection, shock.
- Patients with cardiovascular collapse (shock), acute myocardial infarction, and septicemia
- Metformin is contraindicated in patients with acute or chronic metabolic acidosis such as diabetic ketoacidosis, with or without coma.
- TRIBET must be temporarily discontinued in patients undergoing radiologic studies that require intravascular administration of iodinated contrast materials, since the use of such products may result in acute renal dysfunction.
- Metformin hydrochloride is not recommended for use in pregnancy

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Metformin

Lactic Acidosis

There have been post marketing cases of Metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate: pyruvate ratio; Metformin plasma levels were generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

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

Educate patients and their families about the symptoms of lactic acidosis and, if these symptoms occur, instruct them to discontinue Metformin/Metformin ER and report these symptoms to their healthcare provider.

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

Renal impairment—The postmarketing Metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment.

The risk of Metformin accumulation and Metformin-associated lactic acidosis increases with the severity of renal impairment because Metformin is substantially excreted by the kidney.

Clinical recommendations based upon the patient's renal function include:

Before initiating Metformin/Metformin ER, obtain an estimated glomerular filtration rate (eGFR).

Metformin/Metformin ER is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m2.

Initiation of Metformin/Metformin ER is not recommended in patients with eGFR between 30-45 mL/min/1.73 m2

Obtain an eGFR at least annually in all patients taking Metformin/Metformin ER. In patients at risk for the development of renal impairment(e.g., the elderly), renal function should be assessed more frequently.In patients taking Metformin/Metformin ER whose eGFR falls below 4 5 mL/min/1.73 m2 , assess the benefit and risk of continuing therapy

Drug interactions — The concomitant use of Metformin/Metformin ER 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. Consider more frequent monitoring of patients.

Age 65 or greater — The risk of Metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.

Radiologic studies with contrast — Administration of intravascular iodinated contrast agents in Metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop Metformin/Metformin ER at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m2 ; in patients with a history of hepatic impairment, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart Metformin/Metformin ER 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. Metformin/Metformin ER should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic states — Several of the postmarketing cases of Metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may cause prerenal azotemia. When such an event occurs, discontinue Metformin/Metformin ER.

Excessive alcohol intake — Alcohol potentiates the effect of Metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving Metformin/Metformin ER.

Hepatic impairment — Patients with hepatic impairment have developed cases of Metformin-associated lactic acidosis. This may be due to impaired lactate clearance

resulting in higher lactate blood levels. Therefore, avoid use of Metformin/Metformin ER in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B12 Deficiency

In Metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of Metformin or vitamin B12 supplementation. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. Measure hematologic parameters on an annual basis and vitamin B12 at 2 to 3 year intervals in patients on Metformin/Metformin ER and manage any abnormalities

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues (e.g., sulfonylurea) are known to cause hypoglycemia. Metformin/Metformin ER may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with Metformin/Metformin ER.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Metformin/Metformin ER.

Glimepiride

Hypoglycemia

All sulfonylureas, including Glimepiride, can cause severe hypoglycemia. The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. These impairments may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death.

Patients must be educated to recognize and manage hypoglycemia. Use caution when initiating and increasing Glimepiride doses in patients who may be predisposed to hypoglycemia (e.g., the elderly, patients with renal impairment, patients on other anti-diabetic medications). Debilitated or malnourished patients, and those with adrenal, pituitary, or hepatic impairment are particularly susceptible to the hypoglycemic action of glucose-lowering medications. Hypoglycemia is also more likely to occur when caloric intake is deficient, after severe or prolonged exercise, or when alcohol is ingested.

Early warning symptoms of hypoglycemia may be different or less pronounced in patients with autonomic neuropathy, the elderly, and in patients who are taking beta-adrenergic blocking medications or other sympatholytic agents. These situations may result in severe hypoglycemia before the patient is aware of the hypoglycemia.

Hypersensitivity Reactions

There have been post marketing reports of hypersensitivity reactions in patients treated with Glimepiride, including serious reactions such as anaphylaxis, angioedema, and Stevens-Johnson Syndrome. If a hypersensitivity reaction is suspected, promptly discontinue Glimepiride, assess for other potential causes for the reaction, and institute alternative treatment for diabetes.

Hemolytic Anemia

Sulfonylureas can cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Because Glimepiride is a sulfonylurea, use caution in patients with G6PD deficiency and consider the use of a non-sulfonylurea alternative. There

are also postmarketing reports of hemolytic anemia in patients receiving Glimepiride who did not have known G6PD deficiency

Increased Risk of Cardiovascular Mortality with Sulfonylureas

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2-1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of Glimepiride and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Glimepiride or any other anti-diabetic drug

Pioglitazone

Heart Failure

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 should be observed for signs and symptoms of congestive heart failure. If congestive heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of Pioglitazone must be considered.

Edema

In controlled clinical trials, edema was reported more frequently in patients treated with Pioglitazone than in placebo-treated patients and is dose-related. In post marketing experience, reports of new onset or worsening edema have been received. Pioglitazone should be used with caution in patients with edema. Because thiazolidinediones, including Pioglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, Pioglitazone should be used with caution in patients at risk for congestive heart failure.

Patients treated with Pioglitazone should be monitored for signs and symptoms of congestive heart failure.

Hepatic Effects

There have been post marketing reports of fatal and non-fatal 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.

Patients with type 2 diabetes may have fatty liver disease or cardiac disease with episodic congestive heart failure, both of which may cause liver test abnormalities, and they may also have other forms of liver disease, many of which can be treated or managed. Therefore, obtaining a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) and assessing the patient is recommended before initiating Pioglitazone therapy. In patients with abnormal liver tests, Pioglitazone 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 3 times the upper limit of the reference range), Pioglitazone treatment should be interrupted and investigation done to establish the probable cause. Pioglitazone should not be restarted in these patients without another explanation for the liver test abnormalities.

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

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 difference was noted after the first year of treatment and persisted during the course of the study. The majority of fractures observed in female patients were nonvertebral fractures including lower limb and distal upper limb. No increase in the incidence of fracture was observed in men treated with Pioglitazone (1.7%) versus placebo (2.1%). The risk of fracture should be considered in the care of patients, especially female patients, treated with Pioglitazone and attention should be given to assessing and maintaining bone health according to current standards of care.

Urinary Bladder Tumors

Tumors were observed in the urinary bladder of male rats in the two-year carcinogenicity study. In two 3-year trials in which Pioglitazone was compared to placebo or glyburide, there were 16/3656 (0.44%) reports of bladder cancer in patients taking Pioglitazone compared to 5/3679 (0.14%) in patients not taking Pioglitazone. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six (0.16%) cases on Pioglitazone and two (0.05%) cases on placebo. A five-year interim report of an ongoing 10-year observational cohort study found a nonsignificant increase in the risk for bladder cancer in subjects ever exposed to Pioglitazone, compared to subjects never exposed to Pioglitazone (HR 1.2 [95% CI 0.9 – 1.5]). Compared to never exposure, a duration of Pioglitazone therapy longer than 12 months was associated with an increase in risk (HR 1.4 [95% CI 0.9 – 2.1]), which reached statistical significance after more than 24 months of Pioglitazone use (HR 1.4 [95% CI 1.03 – 2.0]). Interim results from this study suggested that taking Pioglitazone longer than 12 months increased the relative risk of developing bladder cancer in any given year by 40% which equates to an absolute increase of 3 cases in 10,000 (from approximately 7 in 10,000 [without Pioglitazone] to approximately 10 in 10,000 [with Pioglitazone]).

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

Hypoglycemia

Patients receiving PIOGLITAZONE in combination with insulin or other anti-diabetic medications (particularly insulin secretagogues such as sulfonylureas) may be at risk for hypoglycemia. A reduction in the dose of the concomitant anti-diabetic medication may be necessary to reduce the risk of hypoglycemia.

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 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.

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. 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 PIOGLITAZONE is recommended.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Pioglitazone or any other anti-diabetic drug

4.5 DRUGS INTERACTIONS

No	Drug	Drug interaction	Remark
1	**Medications that may DECREASE the glucose-lowering effect of sulfonylureas** oral anti-diabetic medications, pramlintide acetate, insulin, angiotensin converting enzyme(ACE) inhibitors, H2 receptor antagonists, fibrates, propoxyphene, pentoxifylline, somatos tatin analogs, anabolic	These medications' may adversely affect the blood glucose lowering effects of Glimepiride.	These medications affect glucose metabolism and may require Glimepiride dose adjustment and particularly close monitoring for hypoglycemia or worsening glycemic control.

	steroids and androgens, cyclophosphamide, phenyramidol, guanethidine, fluconazole, sulfinpyrazone, tetracyclines, clarithromycin, disopyramide, quinolones **Medications that may DECREASE the glucose-lowering effect of sulfonylureas** Danazol, glucagon, somatropin, protease inhibitors, atypical antipsychotic medications (e.g., olanzapine and clozapine), barbiturates, diazoxide, laxatives, rifampin, thiazides and other diuretics, corticosteroids, phenothiazines, thyroid hormones, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics (e.g., epinephrine, albuterol, terbutaline), and isoniazid.		

2.	Furosemide	*Effect of furosemide on Metformin* Furosemide increases the Metformin plasma and blood Cmax(22% increase) and blood AUC (15% increase) without causing any significant change in Metformin renal clearance. *Effect of Metformin on Furosemide* The Cmax and AUC of furosemide are 31% and 12% lower respectively and the terminal half-life is decreased by 32%, without any significant change in furosemide renal clearance	No data on chronic co administration.
3.	Nifedipine	*Effect of nifedipine on Metformin* Nifedipine increases absorption of Metformin, increases plasma Metformin Cmax and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. Tmax and half-life are unaffected. *Effect of Metformin on nifedipine* Metformin has minimal effects on nifedipine.	
4.	Cationic drugs *(e.g., amiloride,digoxin, morphine, procainamide, quinidine,quinine, cimetidine ranitidine, triamterene, trimethoprim, or vancomycin)* that are eliminated by renal tubular secretion	*Effect of cationic drugs on Metformin* These drugs have the potential for interaction with Metformin by competing for common renal tubular transport systems A 60% increase in peak Metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood Metformin AUC is reported	Careful patient monitoring and dose adjustment of Metformin hydrochloride and/or the interfering drug is recommended
5.	Thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid	These drugs tend to produce hyperglycemia and may lead to loss of glycemic control.	The patient must be closely observed for loss of blood glucose control. When such drugs are withdrawn, the patient should be observed closely for hypoglycemia
6.	Highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid	Glimepiride is highly protein bound drug and can have drug interactions with these drugs Metformin is negligibly bound to plasma proteins and is, therefore, less	The patient must be closely observed for alterations in blood glucose levels.

		likely to interact with highly protein-bound drugs	When these medications are withdrawn from a patient receiving monitor the patient closely for worsening glycemic control.
7.	Miconazole	A potential interaction between oral miconazole and sulfonylureas leading to severe hypoglycemia has been reported	Patient blood glucose monitoring is recommended
8.	Rifampicin	*Effect of rifampicin on Glimepiride* Rifampin may induce the metabolism of Glimepiride, causing decreased plasma concentrations of Glimepiride	Worsening of glycemic control may occur Dose change may be required depending on the change in blood glucose levels
9.	Warfarin	*Effect of Glimepiride on warfarin* Glimepiride causes statistically significant decrease in the pharmacodynamic response to warfarin	Change (increase) in warfarin dose may be required
10.	Propranolol	*Effect of propranolol on Glimepiride* Concomitant administration of propranolol and Glimepiride significantly increases Glimepiride Cmax, AUC, and T ½ by 23%, 22%, and 15%, respectively, and decreases Glimepiride CL/f by 18%.	Monitor blood glucose levels and dose adjustment may be required

4.6 USE IN SPECIAL POPULATIONS (SUCH AS PREGNANT WOMEN, LACTATING WOMEN, PAEDIATRIC PATIENTS, GERIATRIC PATIENTS ETC.)

Renal failure

In patients with mild and moderate renal failure (based on measured creatinine clearance) the oral and renal clearance of Metformin were decreased by 33% and 50% and 16% and 53%, respectively

Before starting Metformin, obtain the patient's eGFR.

Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m^2.

Starting Metformin in patients with an eGFR between 30-45 mL/minute/1.73 m^2 is not recommended Obtain an eGFR at least annually in all patients taking Metformin. In patients at increased risk for the development of renal impairment such as the elderly, renal function should be assessed more frequently.

In patients taking Metformin whose eGFR later falls below 45 mL/minute/1.73 m^2, assess the benefits and risks of continuing treatment. Discontinue Metformin if the patient's eGFR later falls below 30 mL/minute/1.73 m^2.

Discontinue Metformin at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/minute/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 Metformin if renal function is stable.

Hepatic Impairment

No pharmacokinetic studies of Metformin hydrochloride have been conducted in subjects with hepatic insufficiency. It is unknown whether there is an effect of hepatic impairment on Glimepiride pharmacokinetics because the pharmacokinetics of Glimepiride has not been adequately evaluated in patients with hepatic impairment.

Geriatrics

The total plasma clearance of Metformin is decreased, the half-life is prolonged and Cmax is increased in the elderly as compared to healthy young volunteers . This change in Metformin pharmacokinetics in the elderly is attributed to changes in renal function. Metformin treatment must not be initiated in patients 80 years of age unless measurement of creatinine clearance indicates that that renal function is normal.

Monitoring of renal function is required to aid in the prevention of lactic acidosis, especially in the elderly population.

Glimepiride is significantly excreted by the kidney, and the risk of toxic reactions may be increased in elderly patients with impaired renal function. .Care should be taken in dose selection, and it is important to monitor renal function.

Gender: In the pharmacokinetic studies in healthy volunteers, there were no important differences between male and female subjects for either Metformin or Glimepiride.

Pediatrics: There is no pharmacokinetic data available from studies in pediatric subjects of Metformin hydrochloride .Glimepiride has been administered in children 8 to 17 years of age . Glimepiride has been administered at 1mg initially, and then titrated up to 2, 4 or 8 mg.

Surgical procedures

Metformin therapy should be temporarily stopped for any surgical procedure (except minor procedures where restricted intake of food and fluids is not required) and should not be restarted until the patient resumes oral intake and renal function normalizes.

Nursing Mothers

Studies in lactating rats show that Metformin is excreted into milk and reaches levels comparable to those in plasma. Because the potential for hypoglycemia in nursing infants may exist with Glimepiride , and because of the effects on nursing animals, TRIBET should be discontinued in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Driving and using machines This medicine will not affect your ability to drive or use machines but take care if anyone experience abnormal vision.

4.8 UNDESIRABLE EFFECTS

Gastrointestinal disorders:

Vomiting NOS, dyspepsia, flatulence, abdominal pain upper, abdominal distension, loose stools. In 0.7% of patients treated with Metformin hydrochloride + SU, diarrhea was responsible for discontinuation of treatment.

In rare cases, there may be an elevation of liver enzyme levels.

Metabolic complications

Lactic acidosis is a rare but serious reaction that can occur due to Metformin .It is fatal in 50% of cases. Risk factors include renal insufficiency. When Metformin is implicated as the cause of lactic acidosis, Metformin plasma levels > 5 pg/mL are generally found.
The onset of lactic acidosis is associated with nonspecific symptoms such as malaise, myalgias, respiratory distress, nonspecific abdominal distress, increasing somnolence, hypothermia, hypotension and resistant bradyarrhythmias.
Lactic acidosis is characterized by raised blood lactate levels (>5 mmol/L), electrolyte disturbances with an increased anion gap, decreased blood pH, and an increased lactate/pyruvate ratio.
The risk of lactic acidosis may, be significantly decreased by regular monitoring of renal function in patients taking Metformin and by use of the minimum effective dose of Metformin. In particular, treatment of the elderly should be accompanied by careful monitoring
Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis without evidence of ketoacidosis (ketonuria and ketonemia).

Hypoglycemia

The incidence of hypoglycemia with Glimepiride in clinical trials , as documented by blood glucose values <60 mg/dL, ranged from 0.9-1.7%

Hepatic porphyria reactions and disulfiram-like reactions have been reported with sulfonylureas, including Glimepiride. Hyponatremia has reported with Glimepiride / all other sulfonylureas, in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion may occur with sulfonylureas, including Glimepiride. Some sulfonylureas may augment the antidiuretic action of ADH and/or increase release of ADH.

Dermatologic Reactions

Porphyria cutaneatarda, photosensitivity reactions, and allergic vasculitis have been reported with sulfonylureas, including Glimepiride. Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in less than 1% of Glimepiride treated patients. These may be transient and may disappear despite continued use of Glimepiride. If these hypersensitivity reactions persist or worsen (e.g., dyspnea, fall in blood pressure, shock), Glimepiride should be discontinued.

Hematologic Reactions

Leukopenia, agranulocytosis, thrombocytopenia, hemolyticanemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas, including Glimepiride.

Vision disturbances: Changes in accommodation and/or blurred vision may occur with Glimepiride .This may be due to changes in blood glucose, and may be more pronounced when treatment is initiated. These changes are also seen in untreated diabetic patients, and may actually be reduced by treatment.

4.9 OVERDOSE

More intense adverse reactions including epigastric discomfort, nausea, and vomiting followed by diarrhea, drowsiness, weakness, dizziness, malaise and headache may be seen due to Metformin. Should those symptoms persist, lactic acidosis should be excluded. TRIBET must be discontinued and proper supportive therapy must be instituted
Hemodialysis may be useful for removal of accumulated drug from patients in whom Metformin overdosage is suspected. Metformin clearance of up to 170 mL/min can occur under good hemodynamic conditions.

Glimepiride overdosage can produce severe hypoglycemia. Mild episodes of hypoglycemia can be treated with oral glucose. Severe hypoglycemic reactions will require immediate emergency medical treatment.

Severe hypoglycemia can be associated with with coma, seizure, or neurological impairment and can be treated with glucagon or intravenous glucose. Monitoring and additional carbohydrate intake may be necessary because hypoglycemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 MECHANISM OF ACTION

Tribet combines three antihyperglycemic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes: pioglitazone hydrochloride, a member of the thiazolidinedione class, and glimepiride, a member of the sulfonylurea class. Thiazolidinediones are insulin-sensitizing agents that act primarily by enhancing peripheral glucose utilization, whereas sulfonylureas are insulin secretogogues that act primarily by stimulating release of insulin from functioning pancreatic beta cells.

Pioglitazone hydrochloride: Pioglitazone depends on the presence of insulin for its mechanism of action. Pioglitazone decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism. In animal models of diabetes, pioglitazone reduces the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states such as type 2 diabetes. The metabolic changes produced by pioglitazone result in increased responsiveness of insulin-dependent tissues and

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

Glimepiride: The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extrapancreatic effects may also play a role in the activity of sulfonylureas such as glimepiride. This is supported by both preclinical and clinical studies demonstrating that glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin. These findings are consistent with the results of a long-term, randomized, placebo-controlled trial in which glimepiride therapy improved postprandial insulin/C-peptide responses and overall glycemic control without producing clinically meaningful increases in fasting insulin/C-peptide levels. However, as with other sulfonylureas, the mechanism by which glimepiride lowers blood glucose during long-term administration has not been clearly established.

Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves Insulin sensitivity by increasing peripheral glucose uptake and utilization. It thus lowers both basal and postprandial plasma glucose without causing hypoglycemia.

5.2 PHARMACODYNAMICPROPERTIES

Glimepiride and Metformin are oral blood-glucose-lowering drugs used for the management of type 2 diabetes. Glimepiride (sulfonylurea class) is an insulin secretagogue used in the management of type 2 diabetes . Glimepiride selectively closes ATP K+ channels in the functioning beta cells of the pancreas and increases insulin secretion . It does not close the ATP K+ channels in the heart. Metformin hydrochloride (Biguanide class) is an insulin sensitizer. It inhibits the hepatic output of glucose and increases peripheral utilization of glucose. Both Metformin and Glimepiride are used to improve glycemic control in adults with type 2 diabetes mellitus.

5.3 PHARMACOKINETIC PROPERTIES

Co-administration of a single dose of 500 mg Metformin hydrochloride and a did not result in any changes in Metformin pharmacokinetics as AUC; Cmax as well as Tmax were unchanged.

	Metformin	**Glimepiride**
Absorption	The mean Cmax values were 473 ± 145, 868 ± 223, 1171 ± 297, and 1630 ± 399 ng/mL for single doses of 500, 1000, 1500, and 2500 mg For AUC, the mean values were 3501 ± 796, 6705 ± 1918, 9299 ± 2833, and 14161 ± 4432 ng·hr/mL for single doses of 500, 1000, 1500, and 2500 mg, respectively. Low-fat and high-fat meals increased the systemic exposure (as measured by AUC) from Metformin hydrochloride tablets by about 38% and 73%, respectively, relative to fasting	The peak drug concentrations (Cmax) 2 to 3 hours post-dose. When Glimepiride was given with meals, the mean Cmax and AUC (area under the curve) were decreased by 8% and 9%, respectively. The mean AUC at steady state for the older patients is about 13% lower than that for the younger patients
Distribution	The apparent volume of distribution (V/F) of Metformin following single oral doses of 850 mg immediate release Metformin hydrochloride averaged 654 ± 358 L Metformin partitions into erythrocytes, most likely as a function of time.	The volume of distribution (Vd) was 8.8 L (113 mL/kg)
Metabolism	Metformin does not undergo hepatic metabolism	Glimepiride is completely metabolized by oxidative biotransformation. Cytochrome P450 2C9 causes the biotransformation of Glimepiride to cyclohexylhydroxy methyl derivative (M1 derivative).. M1 is further metabolized to the carboxyl derivative M2 by one or several cytosolic enzymes. M2 is inactive

Excretion	Metformin is excreted unchanged in the urine by tubular secretion . Approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours Renal clearance is approximately 3.5 times greater than creatinineclearance.	80-90% of M1 and M2 are recovered in the urine. No parent drug is recovered from urine or feces The mean weight-adjusted clearance for the older patients is about 11% higher than that for the younger patients No biliary excretion has been observed
Half life	In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution	
Plasma protein binding	Negligible	Protein binding is greater than 99.5%.

6. NONCLINICAL PROPERTIES

6.1 ANIMAL TOXICOLOGY OR PHARMACOLOGY

In toxicology studies, plasma volume expansion with haemodilution, anaemia, and reversible eccentric cardiac hypertrophy was consistently apparent after repeated dosing of mice, rats, dogs, and monkeys. In addition, increased fatty deposition and infiltration were observed. These findings were observed across species at plasma concentrations ≤ 4 times the clinical exposure. Foetal growth restriction was apparent in animal studies with pioglitazone. This was attributable to the action of pioglitazone in diminishing the maternal hyperinsulinaemia and increased insulin resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for foetal growth.

Pioglitazone was devoid of genotoxic potential in a comprehensive battery of in vivo and in vitro genotoxicity assays. An increased incidence of hyperplasia (males and females) and tumours (males) of the urinary bladder epithelium was apparent in rats treated with pioglitazone for up to 2 years.

The formation and presence of urinary calculi with subsequent irritation and hyperplasia was postulated as the mechanistic basis for the observed tumourigenic response in the male rat. A 24-month mechanistic study in male rats demonstrated that administration of pioglitazone resulted in an increased incidence of hyperplastic changes in the bladder. Dietary acidification significantly decreased but did not abolish the incidence of tumours. The presence of microcrystals exacerbated the hyperplastic response but was not considered to be the primary cause of hyperplastic changes. The relevance to humans of the tumourigenic findings in the male rat cannot be excluded.

There was no tumorigenic response in mice of either sex. Hyperplasia of the urinary bladder was not seen in dogs or monkeys treated with pioglitazone for up to 12 months.

In an animal model of familial adenomatous polyposis (FAP), treatment with two other thiazolidinediones increased tumour multiplicity in the colon. The relevance of this finding is unknown.

Environmental Risk Assessment (ERA):

No environmental impact is anticipated from the clinical use of pioglitazone.
Metformin:
Preclinical data for metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

7. DESCRIPTION

Tribet® 1:
TRIBET 1 is supplied for oral administration, as an uncoated bilayered tablet of Pioglitazone, Glimepiride and Extended Release Metformin Hydrochloride. Each uncoated bilayered tablet of TRIBET 1 contains Pioglitazone Hydrochloride equivalent to Pioglitazone 15 mg, Glimepiride 1 mg & Metformin Hydrochloride 500mg (as extended release).

Tribet® 2:
TRIBET 2 is supplied for oral administration, as an uncoated bilayered tablet of Pioglitazone, Glimepiride and Extended Release Metformin Hydrochloride. Each uncoated bilayered tablet of TRIBET 2 contains Pioglitazone Hydrochloride equivalent to Pioglitazone 15 mg, Glimepiride 2 mg & Metformin Hydrochloride 500mg (as extended release).

8. PHARMACEUTICAL PARTICULARS

8.1 INCOMPATIBILITIES

Not applicable

8.2 SHELF-LIFE

Refer Pack

8.3 PACKAGING INFORMATION

Refer Pack

8.4 STORAGE CONDITION AND HANDING INSTRUCTIONS

Refer Pack

9. PATIENT COUNSELLING INFORMATION

1. What Tribet is and what it is used for?
   Tribet contains pioglitazone and metformin. It is an anti-diabetic medicine used in adults to treat type 2 (non-insulin dependent) diabetes mellitus when treatment with metformin alone is not sufficient. This type 2 diabetes usually develops in adulthood particularly as a result of the person being overweight and where the body either does not produce enough insulin (a hormone that controls blood sugar levels), or cannot effectively use the insulin it produces. Your doctor will check whether Tribet is working 3 to 6 months after you start taking it. Tribet helps control the level of sugar in your blood when you have type 2 diabetes by helping your body make better use of the insulin it produces.
2. What you need to know before you take Tribet?
   Do not take Tribet - if you are allergic to pioglitazone, metformin or any of the other ingredients of this medicine (listed in section 6). - if you have heart failure or have had heart failure in the past. - if you recently had a heart attack, have severe circulatory

problems including shock, or breathing difficulties. - if you have liver disease. - if you drink alcohol excessively (either every day or only from time to time). - if you have uncontrolled diabetes, with for example severe hyperglycaemia (high blood glucose), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis (see section“Risk of lactic acidosis”) or ketoacidosis. Ketoacidosis is a condition in which substances called 'ketone bodies' accumulate in the blood and which can lead to diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or your breath developing an unusual fruity smell. - if you have or have ever had bladder cancer. - if you have blood in your urine that your doctor has not checked. - if you have severely reduced kidney function. - if you have a severe infection or are dehydrated. 2 - if you are going to have a certain type of X-ray with an injectable dye, talk to your doctor as you must stop taking Tribet for a certain period of time before and after the examination. - if you are breast-feeding. Warnings and precautions Talk to your doctor or pharmacist before taking Tribet (see also section 4). - if you have a problem with your heart. Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin together experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema). - if you retain water (fluid retention) or have heart failure problems in particular if you are over 75 years old. If you take anti-inflammatory medicines which can also cause fluid retention and swelling, you must also tell your doctor. - if you have a special type of diabetic eye disease called macular oedema (swelling of the back of the eye), talk to your doctor if you notice any change to your vision. - if you have cysts on your ovaries (polycystic ovary syndrome). There may be an increased possibility of becoming pregnant because you may ovulate again when you take Tribet. If this applies to you, use appropriate contraception to avoid the possibility of an unplanned pregnancy. - if you have a problem with your liver. Before you start taking Tribet you will have a blood sample taken to check your liver function. This check should be repeated at intervals. Inform your doctor as soon as possible if you develop symptoms suggesting a problem with your liver (like feeling sick without explanations, vomiting, stomach ache, tiredness, loss of appetite and/or dark urine) as your liver function should be checked. You may also experience a reduction in blood count (anaemia). Risk of lactic acidosis Tribet may cause a very rare, but very serious side effect called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration (see further information below), liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease). If any of the above apply to you, talk to your doctor for further instructions. Stop taking Tribet for a short time if you have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instructions. Stop taking Tribet and contact a doctor or the nearest hospital immediately if you experience some of the symptoms of lactic acidosis, as this condition may lead to coma. Symptoms of lactic acidosis include: - vomiting - stomach ache (abdominal pain) - muscle cramps - a general feeling of not being well with severe tiredness - difficulty in breathing - reduced body temperature and heartbeat Lactic acidosis is a medical emergency and must be treated in a hospital. During treatment with Tribet, your doctor will check your kidney function at least once a year or more frequently if you are elderly and/or if you have worsening kidney function. 3 If you need to have major surgery you must stop taking Tribet during and

for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with Tribet. Hypoglycaemia If you take Tribet with other medicines for diabetes, it is more likely that your blood sugar could fall below the normal level (hypoglycaemia). If you experience symptoms of hypoglycaemia such as weakness, dizziness, increased sweating, fast heart-beating, vision disorders or difficulty in concentration, you should take some sugar to increase your blood sugar level again. Ask your doctor or pharmacist for more information if you are not sure how to recognise this. It is recommended that you carry some sugar lumps, sweets, biscuits or sugary fruit juice Broken bones A higher number of bone fractures was seen in patients, particularly women taking pioglitazone. Your doctor will take this into account when treating your diabetes. Children and adolescents Use in children and adolescents under 18 years is not recommended. Other medicines and Tribet If you need to have an injection of a contrast medium that contains iodine into your bloodstream, for example in the context of an X-ray or scan, you must stop taking Tribet before or at the time of the injection. Your doctor will decide when you must stop and when to restart your treatment with Tribet. Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. You may need more frequent blood glucose and kidney function tests, or your doctor may need to adjust the dose of Tribet. It is especially important to mention the following: - gemfibrozil (used to lower cholesterol) - rifampicin (used to treat tuberculosis and other infections) - cimetidine (used to reduce stomach acid) - glucocorticoids (used to treat inflammation) - beta-2-agonists (used to treat asthma) - medicines which increase urine production (diuretics) - medicines used to treat pain and inflammation (NSAID and COX-2-inhibitors, such as ibuprofen and celecoxib) - certain medicines for the treatment of high blood pressure (angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists) Tribet with alcohol Avoid excessive alcohol intake while taking Tribet since this may increase the risk of lactic acidosis (see section “Risk of lactic acidosis”). Pregnancy and breast-feeding - you must tell your doctor if you are pregnant, think you may be pregnant or are planning to have a baby. Tribet is not recommended in pregnancy. If you wish to become pregnant, your doctor will advise you to discontinue this medicine. - do not use Tribet if you are breastfeeding or are planning to breast-feed (see section “Do not take Tribet”). Driving and using machines This medicine will not affect your ability to drive or use machines but take care if you experience abnormal vision. Tribet contains sodium This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

3. How to take Tribet?

   Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. The recommended dose is one tablet taken twice daily. If necessary your doctor may tell you to take a different dose. If you have reduced kidney function, your doctor may prescribe a lower dose, which may need to be given as separate tablets of pioglitazone and metformin. You should swallow the tablets with a glass of water. You may take your tablets with or just after food to reduce the chance of an upset stomach. If you are following a special diet for diabetes, you should continue with this while you are taking Tribet. Your weight should be checked at regular intervals; if your weight increases, inform your doctor. Your doctor will ask you to have blood tests periodically during treatment with Tribet. This is to check that your liver is working normally. At least once a year (more often if you are elderly or have kidney problems) your doctor will check that your kidneys are working normally. If you take more Tribet than you should If you accidentally take too many tablets, or if someone else or a child takes your medicine, talk to a doctor or pharmacist immediately.

Your blood sugar could fall below the normal level and can be increased by taking sugar. It is recommended that you carry some sugar lumps, sweets, biscuits or sugary fruit juice. If you have taken more Tribet that you should have, you may experience lactic acidosis (see section "Risk of lactic acidosis"). If you forget to take Tribet Take Tribet daily as prescribed. However if you miss a dose, skip the missed dose and just carry on with the next dose as normal. Do not take a double dose to make up for a forgotten tablet. If you stop taking Tribet Tribet should be used every day to work properly. If you stop using Tribet, your blood sugar may go up. Talk to your doctor before stopping this treatment. If you have any further questions on the use of this medicine ask your doctor or pharmacist.

4. Possible side effects?

Like all medicines, this medicine can cause side effects, although not everybody gets them. Tribet may cause a very rare (may affect up to 1 in 10,000), but very serious side effect called lactic acidosis (see section "Risk of lactic acidosis"). If this happens you must stop taking Tribet and contact a doctor or the nearest hospital immediately, as lactic acidosis may lead to coma. Bladder cancer has been experienced uncommonly (may affect up to 1 in 100 people) in patients taking Tribet. Signs and symptoms include blood in your urine, pain when urinating or a sudden need to urinate. If you experience any of these, talk to your doctor as soon as possible. Broken bones have been reported commonly (may affect up to 1 in 10 people) in female patients taking Tribet and have also been reported in male patients (frequency cannot be estimated from 5 the available data) taking Tribet. If you experience this side effect, talk to your doctor as soon as possible. Blurred vision due to swelling (or fluid) at the back of the eye (macular oedema) has been reported (frequency cannot be estimated from available data). If you experience these symptoms for the first time talk to your doctor as soon as possible. Also, if you already have blurred vision and the symptoms get worse, talk to your doctor as soon as possible. Allergic reactions have been reported with frequency not known (cannot be estimated from available data) in patients taking Tribet. If you have a serious allergic reaction, including hives and swelling of the face, lips, tongue, or throat that may cause difficulty in breathing or swallowing, stop taking this medicine and talk to your doctor immediately. The following side effects have been experienced by some patients taking Tribet: Very common (may affect more than 1 in 10 people) - stomach ache - feeling sick (nausea) - vomiting - diarrhoea - loss of appetite Common (may affect up to 1 in 10 people) - localised swelling (oedema) - weight gain - headache - respiratory infection - abnormal vision - joint pain - impotence - blood in urine - reduction in blood count (anaemia) - numbness - taste disturbance Uncommon (may affect up to 1 in 100 people) - inflammation of the sinuses (sinusitis) - gas - difficulty sleeping (insomnia) Very rare (may affect up to 1 in 10,000) - decrease in amount of vitamin B12 in the blood - redness of the skin - itchy skin - raised and itchy rash (hives) Not known (frequency can not be estimated from the available data) - inflammation of the liver (hepatitis) - liver does not work as well as it should (changes in liver enzymes) Reporting of side effects If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly to: Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store 6 By reporting side effects you can help provide more information on the safety of this medicine. 5. How to store Tribet Keep this medicine out of the sight and reach of children. Do not use this medicine after the expiry date which is stated on the carton and the blister after "EXP". The expiry date refers to the last day of that month. This medicine does not require any special storage conditions. Do not throw away any medicines via

wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

10. DETAILS OF MANUFACTURER
Refer Pack for manufacturer details.

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Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 6 &
11 to 16 Ground Floor, 101 to 106 &
111 to 116 First Floor, 201 to 206 & 211 to 216
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11. DETAILS OF PERMISSION OR LICENCE NUMBER
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12. DATE OF REVISION
Version 5.0, Dated 27th Sep 2023

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