For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

DIBETA TRIO
Glibenclamide, Pioglitazone and Metformin Hydrochloride (SR) Tablets

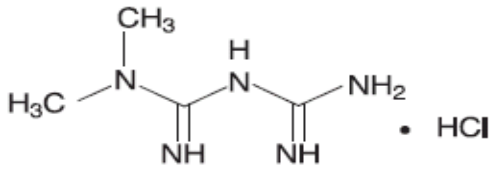
COMPOSITION
DIBETA TRIO
Each uncoated bilayered tablet contains:
Glibenclamide I.P. 5 mg
Pioglitazone Hydrochloride I.P. equivalent to Pioglitazone 15 mg
Metformin Hydrochloride I.P. 500 mg (As sustained release)
Colours: Red Oxide of Iron & Alizarin Cyanine Green F

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.**

DESCRIPTION
Metformin Hydrochloride
Metformin hydrochloride (1, 1-dimethylbiguanide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihypergly-cemic agents. Metformin hydrochloride is a white crystalline powder with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.6. Metformin hydrochloride is freely soluble in water, slightly soluble in ethanol (95 percent), practically insoluble in acetone, in chloroform, in dichloromethane & in

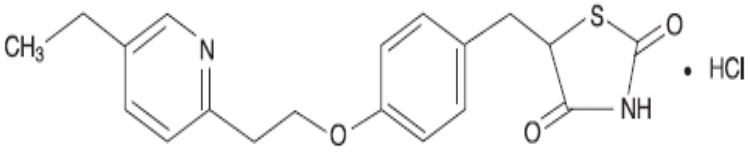
ether. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is as shown:



Pioglitazone Hydrochloride

Pioglitazone hydrochloride is an oral antidiabetic agent that acts primarily by decreasing insulin resistance. Pharmacological studies indicate that Pioglitazone hydrochloride improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Pioglitazone hydrochloride improves glycemic control while reducing circulating insulin levels.

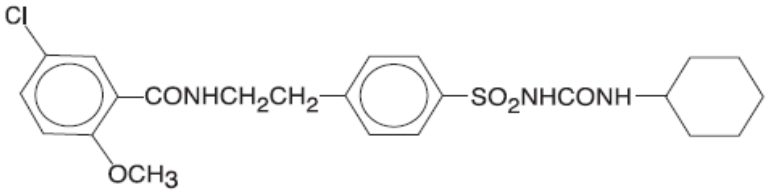
Pioglitazone hydrochloride is (RS)-5-{4-[2-(5-ethyl-2-pyridinyl)ethoxy]benzyl} thiazolidine-2,4-dione hydrochloride belongs to a different chemical class and has a different pharmacological action than the sulfonylureas, metformin, or the α-glucosidase inhibitors. It is used as racemic mixture. The two enantiomers of Pioglitazone interconvert in vivo. No differences were found in the pharmacologic activity between the two enantiomers. The structural formula is as shown:



Pioglitazone hydrochloride is an odorless white crystalline powder that has a molecular formula of $C_{19}H_{20}N_2O_3S$•HCl and a molecular weight of 392.9. It is soluble in N, Ndimethylformamide, very slightly soluble in acetonitrile, practically insoluble in water & in ether.

Glibenclamide

Glibenclamide is an orally active hypoglycaemic agent, which acts by stimulating insulin secretion. It is 1-{4-[2-(5-Chloro-2-methoxybenzamido) ethyl] benzenesulphonyl} -3-cyclohexylurea. It is having a empirical formula $C_{23}H_{28}ClN_3O_5S$ and molecular weight of 494.0. It is sparingly soluble in dichloro methane, slightly soluble in ethanol (95 percent) and in methanol,practically insoluble in water & in ether. It dissolves in dilute solution of alkali hydroxides. The structural formula is:



CLINICAL PHARMACOLOGY

DIBETA TRIO combines three antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: pioglitazone, a member of the thiazolidinedione class, metformin hydrochloride, a member of the biguanide class and glibenclamide, a member of the sulfonylurea class. Thiazolidinediones are insulin-sensitizing agents that act primarily by enhancing peripheral glucose utilization, biguanides act primarily by decreasing endogenous hepatic glucose production while 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 nsulin-dependent glucose disposal and decreased hepatic glucose output. Unlike sulfonylureas, pioglitazone is not an insulin secretagogue. Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPAR-γ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR*y*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.

Metformin hydrochloride

Metformin hydrochloride improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Glibenclamide

The primary mechanism of action of glibenclamide in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells.

Pharmacokinetic

Metformin hydrochloride

A bioequivalence study of metformin 500mg extended release formulation was carried out in healthy volunteers. Mean peak concentrations of extended release Metformin was (C_{max}) 636.9890ng/mL for 500mg dose as compared to reference which had 608.7489ng/ml. Median time to reach peak plasma concentrations (T_{max}) of 5.5 hr was observed. Distribution studies with extended-release metformin have not been conducted. Metformin is negligibly bound to

plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of immediate-release metformin, steady-state plasma concentrations of metformin are reached within 24 - 48 hours and are generally <1 μg/mL.
Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance 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 half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution. Metabolism studies with extended-release metformin tablets have not been conducted. From available literature data for extended release metformin the renal clearance was 542 ± 310 mL/min and dose excreted in urine over 24 hour was 40.9% and for repeated dose no or little accumulation of metformin found in plasma, most of the drug being eliminated via renal route.

Pioglitazone
Following oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Food slightly delays the time to peak serum concentration to 3 to 4 hours, but does not alter the extent of absorption. The mean apparent volume of distribution (V/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. Metabolites M-III and M-IV also are extensively bound (> 98%) to serum albumin. Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-II and M-IV (hydroxy derivatives of pioglitazone) and M-III (keto derivative of pioglitazone) are pharmacologically active in animal models of type 2 diabetes. In addition to pioglitazone, M-III and M-IV are the principal drug-related species found in human serum following multiple dosing. At steady-state, in both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the total peak serum concentrations and 20% to 25% of the total AUC.

In vitro data demonstrate that multiple CYP isoforms are involved in the metabolism of pioglitazone. The cytochrome P450 isoforms involved are CYP2C8 and, to a lesser degree, CYP3A4 with additional contributions from a variety of other isoforms including the mainly extrahepatic CYP1A1. In vivo studies of pioglitazone in combination with P450 inhibitors and substrates have been performed. Urinary 6ß-hydroxy cortisol/cortisol ratios measured in patients treated with pioglitazone showed that pioglitazone is not a strong CYP3A4 enzyme inducer. 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 of pioglitazone and total pioglitazone ranges from 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be 5 to 7 L/hr.

Glibenclamide
Glibenclamide is readily absorbed from the gastrointestinal tract, peak plasma concentrations usually occurring within 2 to 4 hours, and is extensively bound to plasma proteins. Absorption may be slower in hyperglycaemic patients and may differ according to the particle size of the preparation used. It is metabolised, almost completely, in the liver, the principal metabolite being only very weakly active. About 50% of a dose is excreted in the urine and 50% via the bile into the faeces.

Special Populations
Renal Insufficiency
Pioglitazone
The serum elimination half-life of pioglitazone, M-III and M-IV remains unchanged in patients with moderate (creatinine clearance 30 to 60 mL/min) to severe (creatinine clearance < 30 mL/min) renal impairment when compared to normal subjects.

Pediatric Use
Pioglitazone 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.

Metformin hydrochloride
In patients with decreased renal function (based on creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance. Since metformin is contraindicated in patients with renal impairment, combination DIBETA TRIO is also contraindicated in these patients.

Hepatic Insufficiency
Pioglitazone
Patients with impaired hepatic functions (Child-Pugh Grade B/C), pioglitazone mean peak concentration decreased by half but no change in the mean AUC values. Therapy with combination should not be initiated if the patient exhibits clinical evidence of active liver disease or serum transaminase levels (ALT) exceeds 2.5 times the upper limit of normal.

Metformin hydrochloride
No pharmacokinetic studies of metformin have been conducted in subjects with hepatic insufficiency.

Elderly
Pioglitazone
In healthy elderly subjects, peak serum concentrations of pioglitazone and total pioglitazone are not significantly different, but AUC values are slightly higher and the terminal half-life values slightly longer than for younger subjects. These changes were not of a magnitude that would be considered clinically relevant.

Metformin hydrochloride

No data available for extended release formulation of metformin in elderly. Pioglitazone and Metformin combination treatment should not be initiated in patients' ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

Pediatrics

Pioglitazone

Pharmacokinetic data in the pediatric population are not available. Use in pediatric patients is not recommended for the treatment of diabetes due to lack of long-term safety data. Risks including fractures and other adverse effects associated with pioglitazone, one of the components of combination DIBETA Trio, have not been determined in this population.

Metformin hydrochloride

Pharmacokinetic data for extended-release metformin tablets in the pediatric population are not available.

INDICATIONS

DIBETA TRIO is indicated for the treatment of non insulin dependent diabetes (type II), in adult patients, where single patients, where single drug therapy, diet and exercise do no result in adequate glycemic control.

The drug should not be used as first line of therapy for diabetes.

CONTRAINDICATION

• Hypersensitivity to the active substances or to any of the excipients
• Patients with established NYHA class III or IV heart failure
• Acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, shock
• Hepatic impairment
• Acute alcohol intoxication, alcoholism
• Diabetic ketoacidosis or diabetic pre-coma
• Renal failure or renal dysfunction (creatinine clearance <60 ml/min)
• Acute conditions with the potential to alter renal function such as:
• Dehydration
• Severe infection
• Shock
• Intravascular administration of iodinated contrast agents
• Lactation

WARNINGS

Lactic Acidosis

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with pioglitazone hydrochloride and metformin hydrochloride extended-release combination tablets, when it occurs; 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 levels (> 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 μg/mL are generally found.

Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion 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 and by use of the minimum effective dose of metformin. Metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin, since alcohol potentates' the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure. The symptoms of lactic acidosis are malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress and it may be associated with hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and, if indicated, blood pH, lactate levels, and even 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 be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. If lactic acidosis develops, metformin should be immediately discontinued 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.

Increased Risk of Cardiovascular Mortality

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 (Diabetes, 19supp. 2: 747-830, 1970). 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. 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.

Pioglitazone

Cardiac Failure and Other Cardiac Effects

Pioglitazone, like other thiazolidinediones, can cause fluid retention when used alone or in combination with other antihyperglycemic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. Patients should be observed for signs and symptoms of heart failure. If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of pioglitazone must be considered. Pioglitazone should be initiated at the lowest approved dose if it is prescribed for patients with type 2 diabetes and systolic heart failure (NYHA Class II). If subsequent dose escalation is necessary, the dose should be increased gradually only after several months of treatment with careful monitoring for weight gain, edema, or signs and symptoms of congestive heart failure exacerbation.

PRECAUTIONS

General precautions

Pioglitazone

Pioglitazone exerts its antihyperglycemic effect only in the presence of insulin; hence combination should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hypoglycemia

Patients receiving pioglitazone in combination with insulin or oral hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

Cardiovascular

Pioglitazone is not indicated in patients with NYHA Class III or IV cardiac status. Postmarketing experience with pioglitazone, cases of congestive heart failure been reported in both with and without previously known heart disease.

Edema

Edema is reported in placebo controlled trials and is known to be dose-related. Patients should be monitored for sign and symptoms of heart failure during the treatment with pioglitazone hydrochloride.

Weight Gain

Dose related weight gain was observed with pioglitazone alone and in combination with other hypoglycemic agents. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Ovulation

Therapy with pioglitazone, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. Thus, adequate contraception in premenopausal women

should be recommended while taking pioglitazone hydrochloride and metformin hydrochloride combination.

Hematologic
From the clinical trial, pioglitazone decreases the mean haemoglobin level by 2% to 4%. Combination also decreases the haematocrit level.

Hepatic Effects
Therapy with pioglitazone and metformin extended release combination should not be initiated if the patient exhibits clinical evidence of active liver disease or the ALT levels exceed 2.5 times the upper limit of normal. Patients with mildly elevated liver enzymes [ALT levels at 1 to 2.5 UNL (Upper normal limit)] at baseline or any time during therapy with combination should be evaluated to determine the cause of the liver enzyme elevation. Initiation or continuation of therapy with pioglitazone and metformin extended release combination in patients with mildly elevated liver enzymes should proceed with caution and include appropriate clinical follow-up which may include more frequent liver enzyme monitoring. If serum transaminase levels are increased (ALT > 2.5 UNL), liver function tests should be evaluated more frequently until the levels return to normal or pretreatment values. If ALT levels exceed 3 UNL, the test should be repeated as soon as possible. If ALT levels remain > 3 UNL or if the patient is jaundiced, combination should be discontinued.

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 some patients appear to have been diagnosed on routine ophthalmologic examination. Some patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of their thiazolidinedione. It is unknown whether or not there is a causal relationship between pioglitazone and macular edema. Patients with diabetes should have regular eye exams by an ophthalmologist. Additionally, any diabetic who reports any kind of visual symptom should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings.

Fractures
An increased incidence of bone fracture was noted in female patients taking pioglitazone. The majority of fractures observed in female patients were nonvertebral fractures including lower limb and distal upper limb. No increase in fracture rates was observed in men treated with pioglitazone.

Metformin hydrochloride
Monitoring of renal function
Metformin is known to be substantially excreted by the kidney and the risk of Metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive combination. In patients with advanced age, Pioglitazone and metformin extended release combination should be carefully titrated to establish the minimum dose for adequate

glycemic effect, because aging is associated with reduced renal function. In elderly patients, particularly those ≥ 80 years of age, renal function should be monitored regularly and, generally, pioglitazone and Metformin extended release combination should not be titrated to the maximum dose of the metformin component. Before initiation of therapy with combination and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and combination should be discontinued if evidence of renal impairment is present. 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, and use of intravascular iodinated contrast media can lead to acute alteration of renal function which may leads to lactic acidosis while using with metformin. Hence they should be used cautiously.

Hypoxic states
Cardiovascular collapse (shock) from whatever cause, like 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 pioglitazone and metformin extended release combination therapy, the drug should be promptly discontinued.

Surgical procedures
Use of pioglitazone and metformin extended release combination 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.

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 pioglitazone and metformin extended release combination.

Impaired hepatic function
Since impaired hepatic function has been associated with some cases of lactic acidosis, combination should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B12 levels
Metformin is associated with decrease in serum vitamin B12 level. Such decrease, possibly due to interference with B12 absorption from the B12 -intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on pioglitazone and metformin extended release combination 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.

Change in clinical status of patients with previously controlled type 2 diabetes
A patient with type 2 diabetes previously well controlled on pioglitazone and Metformin extended release combination that develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate and metformin levels. If acidosis of either form occurs, combination must be stopped immediately and other appropriate corrective measures initiated

Hypoglycemia
Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is insufficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with hypoglycemic agents (such as sulfonylureas or insulin) or ethanol. 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.

Loss of control of blood glucose
When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold pioglitazone and metformin extended release combination and temporarily administer insulin. Combination may be reinstituted after the acute episode is resolved.

Glibenclamide
Care is necessary in elderly, debilitated or malnourished patients who are particularly susceptible to the hypoglycaemic effects of sulphonylureas, and during excessive exercise as hypoglycaemia may be provoked.

Loss of control of blood glucose
When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. The effectiveness of any oral hypoglycemic drug in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug.

Hemolytic Anemia
Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Because triple combination contains glibenclamide which belongs to the class of sulfonylurea agents, cautionshould be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered. In postmarketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.

ADVERSE EVENTS

Adverse reactions reported during clinical trial of combination are depicted below. Frequencies are defined as: common (> 1/100, < 1/10); uncommon (> 1/1000, < 1/100); rare (>1/10000, < 1/1000); very rare (< 1/10000); isolated reports; not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

PIOGLITAZONE IN COMBINATION THERAPY WITH METFORMIN

Blood and lymphatic system disorders
Common: anaemia

Eye disorders
Common: visual disturbance

Gastrointestinal disorders
Uncommon: flatulence

Metabolism and nutrition disorders
Common: weight increased

Musculoskeletal system and connective tissue disorders
Common: arthralgia

Nervous system disorders
Common: headache

Renal and urinary disorders
Common: haematuria

Reproductive system and breast disorders
Common: erectile dysfunction

POST-MARKETING DATA
Metformin
Metabolism and nutrition disorders:
Very rare: Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloplastic anaemia.
Very rare: Lactic acidosis.

Nervous system disorders:
Common: Taste disturbance

Gastrointestinal disorders:

Very common: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases.

Hepatobiliary disorders:
Isolated reports: Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders:
Very rare: Skin reactions such as erythema, pruritis, and urticaria.

Glibenclamide
Hypoglycaemia occurs with all hypoglycaemic agents. Gastrointestinal disturbances (e.g.: nausea, vomiting, heartburn, anorexia, diarrhoea, metallic taste) are usually mild and dose dependant. Increased appetite and weight gain may occur, also rashes (usually hypersensitivity reactions), pruritus and photosensitivity. Severe manifestations of hypersensitivity include cholestatic jaundice, leucopenia, thrombocytopenia, aplastic anaemia, agranulocytosis, haemolytic anaemia, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis and erythema nodosum. Infrequently a syndrome of inappropriate secretion of antidiuretic hormone may be induced.

Drug Interaction
There are no specific pharmacokinetics data available for pioglitazone, glibenclamide and metformin extended release combination formulation but for individual components data are available.

Pioglitazone
In vivo drug-drug interaction studies have suggested that pioglitazone may be a weak inducer of CYP450 isoform 3A4 substrate.

Oral Contraceptives
No clinically significant pharmacokinetic interaction identified between Pioglitazone and oral contraceptives (e.g. ethinyl estradiol).

Midazolam
Midazolam AUC and Cmax reduced by one-fourth when administered with pioglitazone.

Nifedipine ER
In view of the high variability of nifedipine pharmacokinetics, the clinical significance of interaction between two drugs is unknown.

Gemfibrozil
Concomitant administration of gemfibrozil and pioglitazone resulted in increase exposure of pioglitazone.

Rifampin
When administered concomitantly with pioglitazone, the AUC of the Pioglitazone decrease by half.

Metformin Hydrochloride
Furosemide
Drug-Interaction study of furosemide and metformin results in change in kinetic parameter of both drugs.
Nifedipine
Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic Drugs
Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. -While interaction study (single dose and multiple dose) between metformin and cimetidine results in increase in peak plasma concentration and AUC of metformin but metformin had no effect on cimetidine pharmacokinetic parameter.

Other
Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics –calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving combination formulation, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving combination formulation, the patient should be observed closely for hypoglycemia. No pharmacokinetic interaction was identified of metformin with propranolol or ibuprofen or highly protein bound drugs like salicylates, sulfonamide, chloramphenicol and probenecid.

Glibenclamide
The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including nonsteroidal anti-inflammatory drugs and other drugs that are highly protein bound, such as salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors, and beta adrenergic blocking agents. Due to the potential drug interaction between these drugs and glibenclamide, the patient should be observed closely for hypoglycemia when these drugs are co-administered. Conversely, when these drugs are withdrawn, the patient should be observed closely for loss of glycemic control.

OVERDOSAGE
Pioglitazone
Dose up to 180mg daily for seven days have been reported in literature but no any clinical symptoms seen in patient. In the event of overdosage, appropriate supportive treatment should be initiated according to 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.
Glibenclamide
Overdosage of sulfonylureas, including glibenclamide, can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycemia may recur after apparent clinical recovery.

DOSAGES AND ADMINISTRATION
The use of DIBETA TRIO in the management of type 2 diabetes should be individualized on the basis of effectiveness, tolerability and starting dose as well as current regimen of combination. Selecting the starting dose of DIBETA TRIO should be based on the patient's current regimen of pioglitazone and/or sulfonylurea. Those patients who may be more sensitive to antihyperglycemic drugs should be monitored carefully during dose adjustment. After initiation of DIBETA TRIO, patients should be carefully monitored for adverse events related to fluid retention. It is recommended that a single dose of DIBETA TRIO be administered once daily with the first main meal. The dosage of DIBETA TRIO should gradually titrated, as needed, based on adequacy of the therapeutic response.

The total daily doses of DIBETA TRIO should not exceed the maximum recommended total daily doses of pioglitazone (45mg) or metformin (2000mg for extended release metformin) or glibenclamide (20 mg) Patients should be informed that DIBETA TRIO must be swallowed whole and not chewed, cut or crushed, and that the inactive ingredients may occasionally be eliminated in the feces as a soft mass that resemble the original tablet.

Special Patient Populations
Pregnancy
Pioglitazone, glibenclamide and Metformin extended release combination are not recommended for use during pregnancy, or in breastfeeding women

Geriatric
The initial and maintenance dosing of pioglitazone, glibenclamide and Metformin extended release combination should be conservative in patients with advanced age, due to the potential

for decreased renal function in this population. Any dosage adjustment should be based on a careful assessment of renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of pioglitazone and metformin extended release combination.

Renal Impairment
Metformin is substantially excreted by the kidney. DIBETA TRIO should only be used in patients with normal renal function. Any dosage adjustment in DIBETA TRIO should be based on a careful assessment of renal function.

Hepatic Impairment
Therapy with DIBETA TRIO should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT greater than 2.5 times the upper limit of normal) at start of therapy. Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with DIBETA TRIO and periodically thereafter.

Pediatric
Use in pediatric patients is not recommended for the treatment of diabetes due to lack of long-term safety data.

EXPIRY DATE
Do not use later than the date of expiry.

STORAGE
Store at a temperature not exceeding 30oC, protected from light & moisture.
Keep all medicines out of reach of children

PRESENTATION
DIBETA TRIO is available as blister strips of 10 tablets.

MARKETED BY:

TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

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