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

DIBETA TR
(Metformin Hydrochloride Sustained Release Tablets 500mg and 1000mg)

COMPOSITION
DIBETA TR
Each uncoated sustained release tablet contains:
Metformin Hydrochloride I.P. 500 mg
Excipients q.s.

DIBETA TR 1 GM
Each uncoated sustained release tablet contains:
Metformin Hydrochloride I.P. 1000 mg
Excipients q.s.

INDICATIONS
DIBETA TR as monotherapy is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type-II diabetes. It is also indicated in 17years of age or older. DIBETA TR may be used concomitantly with a sulfonylurea or insulin to improve glycaemic control.

POSOLOGY AND METHOD OF ADMINISTRATION
Adults: There is no fixed dosage regimen for the management of hyperglycemia in patients with type-II diabetes with DIBETA TR or any other pharmacologic agent. Dosage of DIBETA TR should be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose.

The usual starting dose of DIBETA TR is 500 mg once daily with the evening meal. Dosage increases should be made in increments of 500 mg weekly, up to a maximum of 2000 mg once daily with the evening meal. Dose escalation should be gradually for both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycemic control of the patient.

During treatment initiation and dose titration fasting plasma glucose should be used to determine the therapeutic response to DIBETA TR and identify the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin should be measured at intervals of approximately three months. The therapeutic goal should be to decrease both fasting plasma glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dose of DIBETA TR either when used as monotherapy or in combination with sulfonylurea, insulin sensitizers or insulin.

Transfer From Other Antidiabetic Therapy
When transferring patients from the standard oral hypoglycemic agents other than Chlorpropamide to DIBETA TR, no transition period generally is necessary. When patients switching from chlorpropamide therapy to DIBETA TR care should be taken during first two

weeks of therapy because of prolonged retention of Chlorpropamide in the body leading to overlapping drug effects and possible hypoglycemia.

Concomitant DIBETA TR and Sulfonylurea Therapy
If patients have not responded to four weeks of the maximum dose of DIBETA TR or monotherapy, consideration should be given to gradual addition of an oral sulfonylurea while continuing DIBETA TR at the maximum dose, even if prior primary or secondary failure to a sulfonylurea has occurred. With concomitant DIBETA TR and sulfonylurea therapy, the desired control of blood.

glucose may be obtained by adjusting the dose of each drug. If patients have not satisfactorily responded to one to three months of concomitant therapy with the maximum dose of DIABETA TR and the maximum dose of an oral sulfonylurea, consider therapeutic alternatives including switching to insulin with or without DIBETA TR.

Concomitant DIBETA TR and Insulin Therapy in Adult Patients
The current insulin dose should be continued upon initiation of DIBETA TR. DIBETA TR therapy should be initiated at 500 mg once daily in patients on insulin therapy. For patients not responding adequately, the dose of DIBETA TR should be increased by 500 mg after approximately 1 week and by 500 mg every week thereafter until adequate glycemic control is achieved. It is recommended that the insulin dose be decreased by 10% to 25% when fasting plasma glucose concentrations decrease to less than 120 mg/dL in patients receiving concomitant insulin and DIBETA TR. Further adjustment should be individualized based on glucose-lowering response.

Special Populations
Sustained release tablets are not recommended for use in pregnancy and in patients below the age of 17 years. The initial and maintenance dosing of sustained release formulation of Metformin 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 sustained release tablets of Metformin hydrochloride. Monitoring of renal function is necessary to aid in prevention of lactic acidosis, particularly in the elderly.

CONTRAINDICATIONS
• Hypersensitivity to metformin or to any of the excipients
• Moderate (stage 3b) and severe renal failure or renal dysfunction (CrCL < 45 ml/min or eGFR < 45 mL/min/1.73m^2).
• Acute conditions with the potential to alter renal function such as:
- dehydration,
- severe infection,
- shock
• Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as:
- decompensated heart failure,

- respiratory failure,
- recent myocardial infarction,
- shock
• Hepatic insufficiency, acute alcohol intoxication, alcoholism

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Lactic acidosis:

Lactic acidosis is a very rare, but serious (high mortality rate in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with impaired renal failure or acute worsening of renal function. Special caution should be paid to situations where renal function may become impaired, for example in case of dehydration (severe diarrhea or vomiting), or when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID). In the acute conditions listed, metformin should be temporarily discontinued.

Other associated risk factors should be considered to avoid lactic acidosis such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia (such as decompensated cardiac failure, acute myocardial infarction).

The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps, digestive disorders as abdominal pain and severe asthenia. Patients should be instructed to notify these signs immediately to their physicians if they occur, notably if patients had a good tolerance to metformin before. Metformin should be discontinued, at least temporarily, until the situation is clarified. Reintroduction of metformin should then be discussed taking into account the benefit/risk ratio in an individual basis as well as renal function.

Diagnosis:

Lactic acidosis is characterized by acidotic dyspnea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. In case of lactic acidosis, the patient should be hospitalised immediately.

Physicians should alert the patients on the risk and on the symptoms of lactic acidosis.

Renal function:

As metformin is excreted by the kidney, creatinine clearance (this can be estimated from serum creatinine levels by using the Cockcroft-Gault formula) or eGFR should be determined before initiating treatment and regularly thereafter:

• at least annually in patients with normal renal function,

• at least two to four times a year in patients with creatinine clearance levels at the lower limit of normal and in elderly subjects.

In case creatinine clearance CrCl is <45 ml/min (eGFR < 45 ml/min/1.73 m^2), metformin is contraindicated.

Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example in case of dehydration, or when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID).

In these cases, it is also recommended to check renal function before initiating treatment with metformin.

Cardiac function
Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, metformin may be used with a regular monitoring of cardiac and renal function.

For patients with acute and unstable heart failure, metformin is contraindicated.

Administration of iodinated contrast media:
The intravascular administration of iodinated contrast media in radiological studies can lead to renal failure. This may induce metformin accumulation and may increase the risk for lactic acidosis. In patients with eGFR > 60mL/min/1.73m^2, metformin must be discontinued prior to, or at the time of the test and not reinstituted until at least 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further. In patients with moderate renal impairment (eGFR between 45 and 60 ml/min/1.73 m^2), metformin must be discontinued 48 hours before administration of iodinated contrast media and not be reinstituted until at least 48 hours afterwards and only after renal function has been re-evaluated and has not deteriorated further.

Surgery:
Metformin should be discontinued 48 hours before elective surgery with general, spinal or peridural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and only if normal renal function has been established.

Other precautions:
All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.
The usual laboratory tests for diabetes monitoring should be performed regularly.
Metformin alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulphonylureas or meglitinides).
The tablet shells may be present in the faeces. Patients should be advised that this is normal.

DRUG-INTERACTION
Concomitant use not recommended
Alcohol
Acute alcohol intoxication is associated with an increased risk of lactic acidosis in acute alcohol intoxication, particularly in case of:
• fasting or malnutrition,
• hepatic insufficiency.
Avoid consumption of alcohol and alcohol-containing medications.
Iodinated contrast media
Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation and an increased risk of lactic acidosis.

In patients with eGFR > 60mL/min/1.73m^2, metformin must be discontinued prior to, or at the time of the test and not reinstituted until at least 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further.
In patients with moderate renal impairment (eGFR between 45 and 60 ml/min/1.73 m^2), metformin must be discontinued 48 hours before administration of iodinated contrast media and not be reinstituted until at least 48 hours afterwards and only after renal function has been re-evaluated and has not deteriorated further.

Combinations requiring precautions for use
Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics).
More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the other drug and upon its discontinuation.
Diuretics, especially loop diuretics
They may increase the risk of lactic acidosis due to their potential to decrease renal function

FERTILITY, PREGNANCY AND LACTATION
Pregnancy
Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased risk of congenital abnormalities and perinatal mortality.

A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. Animal studies do not indicate harmful effects with respect to pregnancy, embryonic or fetal development, parturition or postnatal development.

When the patient plans to become pregnant and during pregnancy, it is recommended that diabetes is not treated with metformin but insulin be used to maintain blood glucose levels as close to normal as possible to reduce the risk of malformations of the foetus.

Breast-feeding
Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breastfeeding is not recommended during metformin treatment. A decision on whether to discontinue breast-feeding should be made, taking into account the benefit of breast-feeding and the potential risk to adverse effect on the child.

Fertility
Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Metformin monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.

However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (e.g. sulphonylureas, insulin, or meglinitides).

UNDESIRABLE EFFECTS

In post marketing data and in controlled clinical studies, adverse event reporting in patients treated with Metformin SR was similar in nature and severity to that reported in patients treated with METFORMIN immediate release.

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, which resolve spontaneously in most cases.

The following adverse reactions may occur.

Frequencies are defined as follows: very common: >1/10; common ≥1/100, <1/10; uncommon ≥1/1,000, <1/100; rare ≥1/10,000, <1/1,000; very rare <1/10,000.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Metabolism and nutrition disorders

Very rare:

• Lactic acidosis

• Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such an aetiology is recommended if a patient presents with megaloblastic anaemia.

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. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders

Very rare

• Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders

Very rare:

• Skin reactions such as erythema, pruritus, urticaria

OVERDOSE

Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

PHARMACODYNAMIC PROPERTIES

ORAL ANTI-DIABETICS

(A10BA02: Gastrointestinal tract and metabolism)

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Mechanism of action

Metformin may act via 3 mechanisms:

• reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
• in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
• and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT).

Pharmacodynamic effects

In clinical studies, the major non glycemic effect of metformin is either weight stability or modest weight loss.

In humans, independently of its action on glycaemia, immediate release metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: immediate release metformin reduces total cholesterol, LDL cholesterol and triglyceride levels. A similar action has not been demonstrated with the prolonged release formulation, possibly due to the evening administration, and an increase in triglycerides may occur.

Clinical efficacy:

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in overweight type 2 diabetic patients treated with immediate release metformin as first-line therapy after diet failure. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

• a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/ 1000 patient-years) versus diet alone (43.3 events/ 1000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/ 1000 patient-years), p=0.0034.
• a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/ 1000 patient-years, p=0.017;
• a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/ 1000 patient-years versus diet alone 20.6 events/ 1000 patient-years (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/ 1000 patient-years (p=0.021);
• a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/ 1000 patient-years, diet alone 18 events/ 1000 patient-years (p=0.01)

For metformin used as second-line therapy, in combination with a sulphonylurea, benefit regarding clinical outcome has not been shown.

In type 1 diabetes, the combination of metformin and insulin has been used in selected patients, but the clinical benefit of this combination has not been formally established.

Pharmacokinetic properties

Absorption

After an oral dose of the prolonged release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a Tmax at 7 hours (Tmax for the immediate release tablet is 2.5 hours).

At steady state, similar to the immediate release formulation, Cmax and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000mg of metformin prolonged release tablets is similar to that observed after administration of 1000mg of metformin immediate release tablets b.i.d.

Intrasubject variability of Cmax and AUC of metformin prolonged release is comparable to that observed with metformin immediate release tablets.

When the prolonged release tablet is administered in fasting conditions the AUC is decreased by 30% (both Cmax and Tmax are unaffected).

Mean metformin absorption from the prolonged release formulation is almost not altered by meal composition.

No accumulation is observed after repeated administration of up to 2000mg of metformin as prolonged release tablets.

Following a single oral administration of 1500 mg of Metformin SR750 mg, a mean peak plasma concentration of 1193 ng/ml is achieved with a median value of 5 hours and a range of 4 to 12 hours.

Metformin SR750 mg was shown to be bioequivalent to Metformin SR500 mg at a 1500 mg dose with respect to Cmax and AUC in healthy fed and fasted subjects.

Following a single oral administration in the fed state of one tablet of Metformin SR1000 mg, a mean peak plasma concentration of 1214 ng/ml is achieved with a median time of 5 hours (range of 4 to 10 hours).

Metformin SR1000 mg was shown to be bioequivalent to Metformin SR500 mg at a 1000 mg dose with respect to Cmax and AUC in healthy fed and fasted subjects.
When the 1000 mg prolonged release tablet is administered in fed conditions the AUC is increased by 77% (Cmax is increased by 26% and Tmax is slightly prolonged by about 1 hour).

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean Vd ranged between 63-276 L.

Metabolism
Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination
Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Characteristics in specific groups of patients
Renal impairment
The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations.

PRECLINICAL SAFETY DATA
Preclinical data reveal no special hazard for humans based on conventional studies on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity reproduction.

EXPIRY DATE
Do not use from the date of expiry.

STORAGE
KEEP IN A COOL DRY PLACE.
Keep all medicines out of reach of children.

PRESENTATION
Dibeta TR & Dibeta TR 1 GM are available in blister pack of 10 tablets.

MARKETED BY
torrent PHARMA
TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

IN/DIBETA TR 500,1000mg/JAN-2016/01/PI