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

DIBETA SR

1. Generic Name:

Metformin Hydrochloride Sustained Release Tablets IP

2. Qualitative and quantitative composition:

Dibeta SR

Each uncoated sustained release tablet contains:

Metformin Hydrochloride I.P. 500 mg

Dibeta SR 1 GM

Each uncoated sustained release tablet contains:

Metformin Hydrochloride I.P. 1000 mg

The Excipients used are Microcrystalline Cellulose, Povidone, Isopropyl alcohol, Glyceryl dibehenate hydroxyl propyl methyl cellulose.

3. Dosage form and strength:

Dosage form: Uncoated Sustained Release Tablet

Strength: 500 mg, 1000 mg

4. Clinical particulars:

4.1 Therapeutic indication:

Dibeta SR and Dibeta SR 1 GM are used for type II diabetes.

4.2 Posology and method of administration:

Adults with normal renal function (GFR ≥ 90 mL/min)

Reduction in the risk or delay of the onset of type 2 diabetes

- Metformin should only be considered where intensive lifestyle modifications for 3 to 6 months have not resulted in adequate glycaemic control.
- The therapy should be initiated with one tablet Dibeta SR and Dibeta SR 1 GM 500 mg once daily with the evening meal.
- After 10 to 15 days dose adjustment on the basis of blood glucose measurements is recommended (OGTT and/or FPG and/or HbA1C values to be within the normal range). A slow increase of dose may improve gastro-intestinal tolerability. The maximum recommended dose is 4 tablets (2000 mg) once daily with the evening meal.
- It is recommended to regularly monitor (every 3-6 months) the glycaemic status (OGTT and/or FPG and/or HbA1c value) as well as the risk factors to evaluate whether treatment needs to be continued, modified or discontinued.
- A decision to re-evaluate therapy is also required if the patient subsequently implements improvements to diet and/or exercise, or if changes to the medical condition will allow increased lifestyle interventions to be possible.

Monotherapy in Type 2 diabetes mellitus and combination with other oral antidiabetic agents:

- The usual starting dose is one tablet of Dibeta SR and Dibeta SR 1 GM 500 mg once daily.
- After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastro-intestinal tolerability. The maximum recommended dose is 4 tablets daily.
- Dosage increases should be made in increments of 500mg every 10-15 days, up to a maximum of 2000mg once daily with the evening meal. If glycaemic control is not achieved on Dibeta SR and Dibeta SR 1 GM 2000mg once daily, Dibeta SR and Dibeta SR 1 GM 1000mg twice daily should be considered, with both doses being given with food. If glycaemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3000 mg daily.
- In patients already treated with metformin tablets, the starting dose of Dibeta SR and Dibeta SR 1 GM should be equivalent to the daily dose of metformin immediate release tablets. In patients treated with metformin at a dose above 2000 mg daily, switching to Dibeta SR and Dibeta SR 1 GM is not recommended.
- If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate Dibeta SR and Dibeta SR 1 GM at the dose indicated above.
- Dibeta SR and Dibeta SR 1 GM 1000 mg are intended for patients who are already treated with metformin tablets (prolonged or immediate release).
- The dose of Dibeta SR or Dibeta SR and Dibeta SR 1 GM 1000 mg should be equivalent to the daily dose of metformin tablets (prolonged or immediate release), up to a maximum dose of 1500 mg or 2000 mg respectively, given with the evening meal.

Combination with insulin

Metformin and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose of Dibeta SR and Dibeta SR 1 GM is one 500 mg tablet once daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

For patients already treated with metformin and insulin in combination therapy, the dose of Dibeta SR and Dibeta SR 1 GM 1000 mg should be equivalent to the daily dose of metformin tablets up to a maximum of 1500 mg or 2000 mg respectively, given with the evening meal, while insulin dosage is adjusted on the basis of blood glucose measurements.

Elderly

Due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is necessary.

Benefit in the reduction of risk or delay of the onset of type 2 diabetes mellitus has not been established in patients 75 years and older and metformin initiation is therefore not recommended in these patients.

Renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

GFR (mL/min)	Total maximum daily dose	Additional considerations
60-89	2000 mg	Dose reduction may be considered in relation to declining renal function.
45-59	2000 mg	Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin. The starting dose is at most half of the maximum dose.
30-44	1000 mg	
<30	-	Metformin is contraindicated.

In the absence of available data, Dibeta SR should not be used in children.

Dibeta SR and Dibeta SR 1 GM tablet should be swallowed whole and not to be chewed or crushed.

4.3 Contraindications:

Hypersensitivity to metformin or to any of the excipients.

- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma
- Severe renal failure (GFR < 30 mL/min).
- 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

4.4 Special warnings and precautions for use:

Lactic acidosis:

Lactic acidosis, a very rare, but serious, metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis.

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35),

increased plasma lactate levels (>5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.
Renal function: GFR should be assessed before treatment initiation and regularly thereafter, see Metformin is contraindicated in patients with GFR<30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function.

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.

Elderly:

Due to the limited therapeutic efficacy data in the reduction of risk or delay of type 2 diabetes in patients 75 years and older, metformin initiation is not recommended in these patients.

Administration of iodinated contrast agents:

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

Surgery:

Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

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.

This medicine contains less than 1mmol sodium (23mg) per dosage unit that is to say it is essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended

Alcohol

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting, malnutrition or hepatic impairment.

Iodinated contrast agents

Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

Combinations requiring precautions for use

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

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.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of metformin with

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

4.6 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 impaired glycaemic control or diabetes are not treated with metformin. For diabetes it is recommended that insulin should 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.

4.7 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).

4.8 Undesirable effects

In post marketing data and in reported controlled clinical studies, adverse event reporting in patients treated with Dibeta SR and Dibeta SR 1 GM was similar in nature and severity to that reported in patients treated with Glucophage 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 with Dibeta SR and Dibeta SR 1 GM.
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 (see 4.4. Special warnings and precautions for use).
- 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

Reporting of side effects:
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:
https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting

4.9 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.

5. Pharmacological properties:

5.1 Mechanism of Action:

ORAL ANTI-DIABETICS (ATC Code: 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
- 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).

5.2 Pharmacodynamic properties:

In reported 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 reported 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:

Reduction in the risk or delay of type 2 diabetes mellitus

The Diabetes Prevention Program (DPP) was a multicentre randomised controlled reported clinical trial in adults assessing the efficacy of an intensive lifestyle intervention or metformin to prevent or delay the development of type 2 diabetes mellitus. Inclusion criteria were age ≥25 years, BMI ≥24 kg/m2 (≥22 kg/m2 for Asian-Americans), and impaired glucose tolerance plus a fasting plasma glucose of 95 – 125 mg/dl (or ≤125 mg/dl for American Indians). Patients were either treated with intensive lifestyle intervention, 2x850 mg metformin plus standard lifestyle change, or placebo plus standard lifestyle change.

The mean baseline values of the DPP participants (n=3,234 for 2.8 years) were age 50.6±10.7 years, 106.5±8.3 mg/dl fasted plasma glucose, 164.6±17.0 mg/dl plasma glucose two hours after an oral glucose load, and 34.0±6.7 kg/m2 BMI. Intensive lifestyle intervention as well as metformin significantly reduced the risk of developing overt diabetes compared to placebo, 58% (95% CI 48-66%) and 31% (95% CI 17-43%), respectively.

The advantage of the lifestyle intervention over metformin was greater in older persons.

The patients who benefited most from the metformin treatment were aged below 45 years, with a BMI equal or above 35kg/m2, a baseline glucose 2 h value of 9.6-11.0 mmol/l, a baseline HbA1C equal or above 6.0% or with a history of gestational diabetes.

To prevent one case of overt diabetes during the three years in the whole population of the DPP, 6.9 patients had to participate in the intensive lifestyle group and 13.9 in the metformin group. The

point of reaching a cumulative incidence of diabetes equal to 50% was delayed by about three years in the metformin group compared to placebo.

The Diabetes Prevention Program Outcomes Study (DPPOS) is the reported long-term follow-up study of the DPP including more than 87% of the original DPP population for long-term follow up.

Among the DPPOS participants (n=2776), the cumulative incidence of diabetes at year 15 is 62% in the placebo group, 56% in the metformin group, and 55% in the intensive lifestyle intervention group. Crude rates of diabetes are 7.0, 5.7 and 5.2 cases per 100 person-years among the placebo, metformin, and intensive lifestyle participants, respectively. Reductions in the diabetes risk were of 18% (hazard ratio (HR) 0.82, 95% CI 0.72–0.93; p=0.001) for the metformin group and 27% (HR 0.73, 95% CI 0.65–0.83; p<0.0001) for the intensive lifestyle intervention group, when compared with the placebo group. For an aggregate microvascular endpoint of nephropathy, retinopathy and neuropathy, the outcome was not significantly different between the treatment groups, but among the participants who had not developed diabetes during DPP/DPPOS, the prevalence of the aggregate microvascular outcome was 28% lower compared with those who had developed diabetes (Risk Ratio 0.72, 95% CI 0.63–0.83; p<0.0001). No prospective comparative data for metformin on macrovascular outcomes in patients with IGT and/or IFG and/or increased HbA1C are available.

Published risk factors for type 2 diabetes include: Asian or black ethnic background, age above 40, dyslipidaemia, hypertension, obesity or being overweight, age, 1st degree family history of diabetes, history of gestational diabetes mellitus, and polycystic ovary syndrome (PCOS).

Consideration must be given to current national guidance on the definition of prediabetes.

Patients at high risk should be identified by a validated risk-assessment tool.

Treatment of type 2 diabetes mellitus

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.

5.3 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 in the fed state of one tablet of Dibeta SR and Dibeta SR 1 GM 1000 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).

Dibeta SR and Dibeta SR 1 GM 1000 mg was shown to be bioequivalent to Dibeta SR and Dibeta SR 1 GM 500 mg at a 1000 mg dose with respect to C_{max} 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% (C_{max} is increased by 26% and T_{max} 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

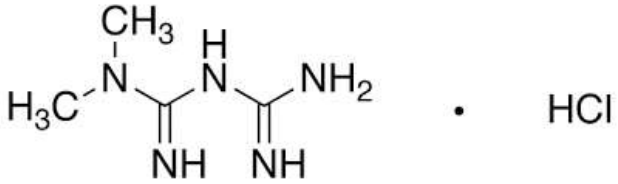
The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability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

6. Nonclinical properties:

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

7. Description:

Metformin Hydrochloride is 1, 1-dimethylbiguanide hydrochloride. The empirical formula is $C_4H_{11}N_5$. HCL and its molecular weight is 165.6 g/mol. The chemical structure of Metformin Hydrochloride is:



8. Pharmaceutical particulars:

8.1 Incompatibilities:

Not applicable.

8.2 Shelf-life:

Do not use later than the date of expiry.

8.3 Packaging information:

Dibeta SR and Dibeta SR 1 GM is available in Blister pack of 10 tablets.

8.4 Storage and handing instructions:

Dibeta SR and Dibeta SR 1 GM Store in a dry place at a temperature not exceeding 25^o C, protected from light. Keep all medicines out of reach of children.

9 Patient Counselling Information

Package leaflet: Information for the user

Dibeta SR and Dibeta SR 1 GM

(Metformin Hydrochloride Sustained Release Tablets IP)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.5 How to store **Dibeta SR and Dibeta SR 1 GM**
9.6 Contents of the pack and other information

9.1 What Dibeta SR and Dibeta SR 1 GM is and what it is used for

Dibeta SR and Dibeta SR 1 GM prolonged release tablets contain the active ingredient metformin hydrochloride and belong to a group of medicines called biguanides, used in the treatment of Type 2 (non-insulin dependent) diabetes mellitus.

Dibeta SR and Dibeta SR 1 GM is used together with diet and exercise to lower the risk of developing Type 2 diabetes in overweight adults, when diet and exercise alone for 3 to 6 months have not been enough to control blood glucose (sugar). You are at high risk of developing Type 2 diabetes if you have additional conditions like high blood pressure, age above 40 years, an abnormal amount of lipids (fat) in the blood or a history of diabetes during pregnancy.

The medicine is particularly effective if you are aged below 45 years, are very overweight, have high blood glucose levels after a meal or developed diabetes during pregnancy.

Dibeta SR and Dibeta SR 1 GM is used for the treatment of Type 2 diabetes when diet and exercise changes alone have not been enough to control blood glucose (sugar). Insulin is a hormone that enables body tissues to take glucose from the blood and to use it for energy or for storage for future use. People with Type 2 diabetes do not make enough insulin in their pancreas or their body does not respond properly to the insulin it does make. This causes a build-up of glucose in the blood which can cause a number of serious long-term problems so it is important that you continue to take your medicine, even though you may not have any obvious symptoms. Dibeta SR and Dibeta SR 1 GM makes the body more sensitive to insulin and helps return to normal the way your body uses glucose.

Dibeta SR and Dibeta SR 1 GM is associated with either a stable body weight or modest weight loss. Dibeta SR and Dibeta SR 1 GM Prolonged Release Tablets are specially made to release the drug slowly in your body and therefore are different to many other types of tablet containing metformin.

9.2 What you need to know before you take Dibeta SR and Dibeta SR 1 GM

- Do not take Dibeta SR and Dibeta SR 1 GM if:
- you are allergic to metformin or to any of the other ingredients of this medicine. An allergic
- reaction may cause a rash, itching or shortness of breath.
- you have liver problems
- you have severely reduced kidney function
- you have uncontrolled diabetes, with, for example, severe hyperglycaemia (high blood glucose), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis (see ‘Risk of lactic acidosis’ below) 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.
- you have lost too much water from your body (dehydration). Dehydration may lead to kidney problems, which can put you at risk for lactic acidosis (see 'Warnings and precautions').
- you have a severe infection, such as an infection affecting you lung or bronchial system or your kidney. Severe infections may lead to kidney problems, which can put you at risk for lactic acidosis.
- you have been treated for acute heart problems or have recently had a heart attack or have severe circulatory problems or breathing difficulties. This may lead to a lack in oxygen supply to tissue

which can put you at risk for lactic.
- you are a heavy drinker of alcohol.
- you are under 18 years of age.

Warnings and precautions
Risk of lactic acidosis
Dibeta SR and Dibeta SR 1 GM 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 Dibeta SR and Dibeta SR 1 GM 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 Dibeta SR and Dibeta SR 1 GM 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.
If you need to have major surgery you must stop taking Dibeta SR and Dibeta SR 1 GM during and for some time after the procedure.
Your doctor will decide when you must stop and when to restart your treatment with Dibeta SR and Dibeta SR 1 GM.
During treatment with Dibeta SR and Dibeta SR 1 GM, 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.
If you are older than 75 years, treatment with Dibeta SR and Dibeta SR 1 GM should not be started to lower the risk of developing type 2 diabetes.
You may see some remains of the tablets in your stools. Do not worry- this is normal for this type of tablet.
You should continue to follow any dietary advice that your doctor has given you and you should make sure that you eat carbohydrates regularly throughout the day.
Do not stop taking this medicine without speaking to your doctor.

Other medicines and Dibeta SR and Dibeta SR 1 GM
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 Dibeta SR and Dibeta SR 1 GM before or at the time of injection. Your doctor will decide when you must stop and when to restart your treatment with Dibeta SR and Dibeta SR 1 GM.
Tell your doctor 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 dosage of Dibeta SR and Dibeta SR 1 GM. It is especially important to mention the following:
- Medicines which increase urine production (diuretics (water tablets) such as furosemide).

- 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 (ACE inhibitors and angiotensin II receptor antagonists)
- Steroids such as prednisolone, mometasone, beclometasone.
- Sympathomimetic medicines including epinephrine and dopamine used to treat heart attacks and low blood pressure. Epinephrine is also included in some dental anaesthetics.
- Medicines that may change the amount of Dibeta SR and Dibeta SR 1 GM in your blood, especially if you have reduced kidney function (such as verapamil, rifampicin, cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole, crizotinib, olaparib).

Dibeta SR and Dibeta SR 1 GM with alcohol
Avoid excessive alcohol intake while taking Dibeta SR and Dibeta SR 1 GM since this may increase the risk of lactic acidosis.

Pregnancy and breast-feeding
Do not take Dibeta SR and Dibeta SR 1 GM if you are pregnant or breast feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Dibeta SR and Dibeta SR 1 GM taken on its own does not cause 'hypos' (symptoms of low blood sugar or hypoglycaemia, such as faintness, confusion and increased sweating) and therefore should not affect your ability to drive or use machinery.
You should be aware, however, that Dibeta SR and Dibeta SR 1 GM taken with other antidiabetic medicines can cause hypos, so in this case you should take extra care when driving or operating machinery.

Information about ingredient of Dibeta SR and Dibeta SR 1 GM
This medicine contains less than 1mmol sodium (23mg) per dosage unit that is to say it is essentially 'sodium free'.

9.3 How to take Dibeta SR and Dibeta SR 1 GM

Your doctor may prescribe Dibeta SR and Dibeta SR 1 GM for you to take on its own, or in combination with other oral antidiabetic medicines or insulin.
Always take Dibeta SR and Dibeta SR 1 GM exactly as your doctor has told you.
You should check with your doctor or pharmacist if you are not sure.
Swallow the tablets whole with a glass of water, do not chew.

Recommended dose
Usually you will start treatment with 500 milligrams Dibeta SR and Dibeta SR 1 GM daily. After you have been taking Glucophage.
SR for about 2 weeks, your doctor may measure your blood sugar and adjust the dose. The maximum daily dose is 2000 milligrams of Dibeta SR and Dibeta SR 1 GM.
If you have reduced kidney function, your doctor may prescribe a lower dose.
Normally, you should take the tablets once a day, with your evening meal.
In some cases, your doctor may recommend that you take the tablets twice a day. Always take the tablets with food.
If you take extra tablets by mistake you need not worry, but if you have unusual symptoms, contact your doctor. If the overdose is large, lactic acidosis is more likely. Symptoms of lactic acidosis are non-specific, such as vomiting, bellyache with muscle cramps, a general feeling of not being well

with severe tiredness, and difficulty in breathing. Further symptoms are reduced body temperature and heartbeat. If you experience some of these symptoms, you should immediately seek medical attention, as lactic acidosis may lead to coma. Stop taking Dibeta SR and Dibeta SR 1 GM immediately and contact a doctor or the nearest hospital straightaway.

If you forget to take Dibeta SR and Dibeta SR 1 GM

Take it as soon as you remember with some food. Do not take a double dose to make up for a forgotten dose.

9.4 Possible side effects

Like all medicines, Dibeta SR and Dibeta SR 1 GM can cause side effects, although not everybody gets them. The following side effects may occur:

Dibeta SR and Dibeta SR 1 GM may cause a very rare (may affect up to 1 user in 10,000) but very serious side effect called lactic acidosis. If this happens, you must stop taking the Dibeta SR and Dibeta SR 1 GM and contact a doctor or the nearest hospital immediately, as lactic acidosis may lead to coma.

Dibeta SR and Dibeta SR 1 GM may cause abnormal liver function tests and hepatitis (inflammation of the liver) which may result in jaundice (may affect up to 1 user in 10,000). If you develop yellowing of the eyes and/or skin contact your doctor immediately.

Other possible side effects are listed by frequency as follows:

Very common (affects more than 1 person in 10): Diarrhoea, nausea, vomiting, stomach ache or loss of appetite. If you get these, do not stop taking the tablets as these symptoms will normally go away in about 2 weeks. It helps if you take the tablets with or immediately after a meal.

Common (affects less than 1 person in 10, but more than 1 person in 100):

- Taste disturbance

Very rare (affects less than 1 person in 10,000):

- Decreased vitamin B12 levels
- Skin rashes including redness, itching and hives

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting

9.5 How to store Dibeta SR and Dibeta SR 1 GM

- Keep Dibeta SR and Dibeta SR 1 GM tablets out of the sight and reach of children.
- Do not use them after the expiry date that is printed on the pack after “EXP:” The expiry date refers to the last day of that month.
- This medicinal product does not require any special storage conditions.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

9.6 Contents of the pack and other information

What the tablets contain

Each prolonged release tablet contains 500 and1000 milligrams of the active ingredient metformin hydrochloride. The other ingredients are magnesium stearate, carmellose sodium and hypromellose.

Dibeta SR and Dibeta SR 1 available in Blister pack 10 tablets.

10. Details of manufacturer

Dibeta SR

TORRENT PHARMACEUTICALS LTD.

32 No. Middle camp, NH 10,

East district, Gangtok, Sikkim-737 135

Dibeta SR 1 GM

TORRENT PHARMACEUTICALS LTD.

32 No. Middle camp, NH 10,

East district, Gangtok, Sikkim-737 135

OR

Pure & Cure Healthcare Pvt. Ltd.

Plot No. 26a, 27-30, Sector-8A, I.I.E, SIDCUL,

Ranipur, Haridwar-249403,

Uttarakhand.

11. Details of permission or licence number with date

DIBETA SR

TORRENT PHARMACEUTICALS LTD.

M/563/2010 issued on 12.06.2018

Dibeta SR 1 GM

TORRENT PHARMACEUTICALS LTD.

M/563/2010 issued on 23.12.2026

OR

Pure & cure Healthcare Pvt. Ltd.

Mfg Lic No. 31/UA/2013 issued on 14.10.2020

12. Date of revision

AUG 2021

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

Torrent House, Off Ashram Road,

Ahmedabad-380 009, INDIA

IN/DIBETA SR 500, 1000mg/AUG-21/02/PI