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

Prescribing Information

1. Generic Name

Dapagliflozin Tablets and Metformin Hydrochloride (Extended release) Tablets
(Brand Name: Diabiz®-M Tablets and Diabiz®-M Forte Tablets)

2. Qualitative and Quantitative Composition

DIABIZ® -M Tablets
Each film-coated Bilayered tablet contains:
Dapagliflozin Propanediol Monohydrate equivalent to Dapagliflozin …… 10 mg.
Metformin Hydrochloride IP (Extended release) ……..… 500 mg.
Excipients …… q.s.
Colour: Erythrosine Lake (In Dapagliflozin Layer)

DIABIZ® -M Forte Tablets
Each film-coated Bilayered tablet contains:
Dapagliflozin Propanediol Monohydrate equivalent to Dapagliflozin …… 10 mg.
Metformin Hydrochloride IP (Extended release) ……..…..… 1000 mg.
Excipients …… q.s.
Colour: Yellow Oxide of Iron. (In Dapagliflozin Layer)

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength:
10 mg Dapagliflozin/500 mg Metformin HCl Extended release
10 mg Dapagliflozin/1000 mg Metformin HCl Extended release

4. Clinical Particulars

4.1 Therapeutic Indication

Type 2 Diabetes
DIABIZ Tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and when monotherapy treatment with dapagliflozin and metformin is insufficient.

4.2Posology and Method of Administration

For oral administration in adults.

Assess renal function prior to initiation of dapagliflozin therapy and then as clinically indicated. Assess volume status and, if necessary, correct volume depletion prior to initiation of dapagliflozin therapy.

DIABIZ-M Tablets: Usual recommended dose in adults with type 2 diabetes is 1 tablet orally once daily.
DIABIZ-M Forte Tablets: Usual recommended dose in adults is 1 tablet orally once daily, preferably in overweight or obese type 2 diabetic patients.
DIABIZ-M and DIABIZ-M Forte Tablets can be administered with or without a meal. However, taking tablets with or just after food may reduce gastrointestinal symptoms associated with metformin. Swallow tablet whole with water and strictly not to cut, crush or chew.
Or, as prescribed by the Physician.

4.3Contraindications

DIABIZ-M Tablets and DIABIZ-M Forte Tablets are contraindicated in the following:

- Known hypersensitivity to dapagliflozin or to metformin or to any components of the formulation.
- Type 1 diabetic patient.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.
- Patients with severe infection, surgery, severe trauma (it is advised to control blood glucose level by insulin).
- Acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism (due to the metformin component).
- Severe renal impairment (eGFR below 30 ml/min/1.73 m^2).
- Patients on dialysis.

4.4Special Warnings and Precautions for Use

Dapagliflozin

Ketoacidosis in Patients with Diabetes Mellitus
Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in patients with type 1 and type 2 diabetes mellitus receiving sodium-glucose co-transporter 2 (SGLT2) inhibitors, including dapagliflozin.
In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. Fatal cases of ketoacidosis have been reported in patients taking dapagliflozin.
Before initiating dapagliflozin, consider factors in the patient history that may predispose to ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing dapagliflozin for at least 3 days prior to surgery. Consider monitoring for ketoacidosis and temporarily discontinuing dapagliflozin in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting dapagliflozin.
Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue dapagliflozin and seek medical attention immediately if signs and symptoms occur.

Volume Depletion
Dapagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including dapagliflozin. Patients with impaired renal function (estimated glomerular filtration rate - eGFR less than 60 ml/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating dapagliflozin in patients with one or more of these characteristics, assess volume status and renal function. Monitor for signs and symptoms of hypotension, and renal function after initiating therapy.

Urosepsis and Pyelonephritis
Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been reported in patients receiving SGLT2 inhibitors, including dapagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
Insulin and insulin secretagogues are known to cause hypoglycemia. Dapagliflozin may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with dapagliflozin.

Necrotizing Fasciitis of the Perineum
Reports of necrotizing fasciitis of the perineum (Fournier Gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in post-marketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including dapagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.
Patients treated with dapagliflozin presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue dapagliflozin, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections
Dapagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections; monitor such patients and treat appropriately.

Metformin

Lactic Acidosis: Lactic acidosis is a rare, but serious (high mortality 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 significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency, and any condition associated with hypoxia. If metformin-associated lactic acidosis is suspected, immediately discontinue metformin therapy and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.
The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.

Excessive Alcohol Intake: Alcohol is known to potentiate the effect of metformin on lactate metabolism. Acute alcohol intoxication is associated with an increased risk of lactic acidosis. Warn patients against excessive alcohol intake while receiving metformin therapy.

Radiologic Studies with Iodinated Contrast Media: Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. Metformin hydrochloride must be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Hypoxic States: Cardiovascular collapse (shock) of any kind, 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 on metformin therapy, the drug should be promptly discontinued.

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.

Renal Function: As metformin is excreted by the kidney, creatinine clearance should be determined before initiating treatment and regularly thereafter at least annually in patients with normal renal function and at least 2 to 4 times a year in patients with creatinine clearance levels at the upper limit of normal and in elderly subjects.

Loss of Blood Glucose Control: 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 oral antidiabetic agents and temporarily administer insulin. Metformin may be reinstituted after the acute episode is resolved.

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 when normal renal function has been established.
Hepatic Impairment: Patients with hepatic impairment have developed cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of metformin in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B12 Deficiency: Long-term use of metformin may decrease absorption of vitamin B12 with resultant decrease in plasma B12 levels. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, may be associated with anemia, but appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. It is recommended to measure hematologic parameters on an annual basis and vitamin B12 at 2 to 3 year intervals in patients on metformin therapy.

Other Precautions: The usual laboratory tests for diabetes monitoring should be performed regularly. Metformin alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetic drugs.

4.5Drug Interactions

Dapagliflozin

Pharmacodynamic Interactions
Diuretics: Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.
Insulin and insulin secretagogues: Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, in patients with type 2 diabetes mellitus, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with dapagliflozin.

Pharmacokinetic Interactions
The metabolism of dapagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyltransferase 1A9 (UGT1A9).
In *in vitro* studies, dapagliflozin neither inhibited cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, nor induced CYP1A2, CYP2B6 or CYP3A4.

Therefore, dapagliflozin is not expected to alter the metabolic clearance of co-administered medicinal products that are metabolized by these CYP enzymes.

Effect of other medicinal products on dapagliflozin
Pharmacokinetics of dapagliflozin are not altered by metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.
Following co-administration of dapagliflozin with rifampicin (an inducer drug-metabolizing enzyme) a 22% decrease in dapagliflozin systemic exposure (area under the plasma concentration of a drug versus time curve - AUC) was observed, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended. A clinically relevant effect with other CYP inducers (e.g., carbamazepine, phenytoin, phenobarbital, etc.) is not expected.
Following co-administration of dapagliflozin with mefenamic acid (an inhibitor of UGT1A9), a 55% increase in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended.

Effect of dapagliflozin on other medicinal products
Dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, digoxin, or warfarin (or the anticoagulatory effects of warfarin). Combination of a single dose of dapagliflozin 20 mg and simvastatin (a CYP3A4 substrate) resulted in a 19% increase in AUC of simvastatin and 31% increase in AUC of simvastatin acid. The increase in simvastatin and simvastatin acid exposures are not considered clinically relevant.

Interference with 1,5-anhydroglucitol (1,5-AG) assay: Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use of alternative methods to monitor glycemic control is advised.
Positive urine glucose test: Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Metformin

Carbonic Anhydrase Inhibitors (e.g., topiramate, zonisamide, acetazolamide or dichlorphenamide): Carbonic anhydrase inhibitors frequently cause a decrease in serum bicarbonate and induce hyperchloremic non-anion gap metabolic acidosis. Concomitant use of these drugs with metformin may increase the risk for lactic acidosis. More frequent monitoring of these patients is recommended.

Drugs that Reduce Metformin Clearance (e.g., ranolazine, vandetanib, dolutegravir, and cimetidine): Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors) could increase systemic exposure to metformin and may increase the risk for lactic acidosis.

Drugs Affecting Glycemic Control (e.g., thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid): These drugs tend to produce hyperglycemia and may lead to loss of glycemic control. When these drugs are administered to a patient receiving metformin, observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving metformin, observe the patient closely for hypoglycemia.

Insulin Secretagogues or Insulin: Co-administration of metformin with an insulin secretagogue (e.g., sulfonylurea) or insulin may increase the risk of hypoglycemia. Patients receiving an insulin secretagogue or insulin may require lower doses of the insulin secretagogue or insulin.

Combinations Requiring Precautions for Use:

1. Some drugs may adversely affect renal function which may increase the risk of lactic acidosis, e.g., NSAIDs, including selective cyclooxygenase (COX)-2 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.
2. Glucocorticoids (systemic and local routes), beta 2-agonists, and diuretics have intrinsic hyperglycemic activity. More frequent blood glucose monitoring, especially at the beginning of treatment is required. If necessary, adjust the metformin dosage during therapy with these drugs and upon its discontinuation.

ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the metformin dosage during therapy with these drugs and upon its discontinuation.

4.6Use in Special Populations

Pregnancy: There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactating women: Discontinue DIABIZ-M/DIABIZ-M Forte tablets or discontinue nursing.

Geriatrics: Higher incidence of adverse reactions related to reduced intravascular volume. Assess renal function more frequently.

Renal Impairment: Higher incidence of adverse reactions related to reduced intravascular volume and renal function.

Hepatic Impairment: Avoid use in patients with hepatic impairment.

4.7Effect on Ability to Drive and Use Machines

Data is not available on the effects of dapagliflozin with metformin combination therapy on ability to drive and use machines. Patients who experience dizziness as an adverse reaction should avoid driving vehicles or using machines. Further, patients should be cautioned about the risk of hypoglycaemia especially when this medicine is co-administered with sulphonylurea and/or insulin.

4.8Undesirable Effects

Dapagliflozin

The most common adverse reactions reported with dapagliflozin are ketoacidosis in diabetic patients, volume depletion, urosepsis and pyelonephritis, hypoglycemia when co-prescribed with insulin and insulin secretagogues, necrotizing fasciitis of the perineum, and genital mycotic infections.

The following adverse reactions have been identified from the clinical trials and post-marketing surveillance studies; none of them are found to be dose-related. Adverse reactions are classified according to frequency and system organ class (SOC). Frequency of these reactions are defined according to the following criteria: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data).

Infections and Infestations: Common: Vulvovaginitis, balanitis and related genital infections, urinary tract infection; Uncommon: Fungal infections; Very Rare: Necrotising fasciitis of the perineum (Fournier's gangrene).

Metabolism and Nutrition Disorders: Very Common: Hypoglycaemia (when used with sulphonylureas or insulin); Uncommon: Volume depletion (dehydration, hypovolaemia, hypotension), thirst; Rare: Diabetic ketoacidosis.

Nervous System Disorders: Common: Dizziness.

Gastrointestinal Disorders: Uncommon: Constipation, dry mouth.

Skin and Subcutaneous Tissue Disorders: Common: Rash; Very Rare: Angioedema.

Musculoskeletal and Connective Tissue Disorders: Common: Back pain.

Renal and Urinary Disorders: Common: Dysuria, polyuria; Uncommon: Nocturia, acute kidney injury.

Reproductive System and Breast Disorders: Uncommon: Vulvovaginal pruritus, genital pruritus.

Investigations: Common: Increased haematocrit, increased serum creatinine, decreased eGFR, decreased creatinine renal clearance during initial treatment, dyslipidaemia; Uncommon: Increased blood creatinine during initial treatment, increased blood urea, decreased body weight; Rare: Increased low-density lipoprotein cholesterol (LDL-C) levels.

Metformin

The most common adverse reactions reported with metformin are nausea, vomiting, diarrhoea, indigestion, abdominal pain, abdominal discomfort, constipation, dyspepsia/heartburn, flatulence, dizziness, taste disturbance, headache, upper respiratory infection, asthenia, and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. Very rarely metformin may cause skin reactions such as erythema, pruritus, urticaria; abnormal liver function test or hepatitis; and lactic acidosis which generally resolve upon metformin discontinuation.

Cholestatic, hepatocellular, and mixed hepatocellular liver injury have been reported with post-marketing use of metformin.

4.9Overdose

Dapagliflozin

There were no reports of overdosage with dapagliflozin. In clinical studies, dapagliflozin did not show any toxicity in healthy subjects at single oral doses up to 500 mg (50-times the maximum recommended human dose). In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. The removal of dapagliflozin by haemodialysis has not been studied.

Metformin

Overdose of metformin hydrochloride has been reported with ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. Lactic acidosis is a medical emergency and must be treated in hospital. Metformin is dialyzable, with a clearance of up to 170 ml/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of the accumulated drug from patients in whom metformin overdose is suspected.

5. Pharmacological Properties

5.1 Mechanism of Action

Dapagliflozin

Dapagliflozin is a highly potent, selective, and reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2). The SGLT2 is selectively expressed in the proximal renal tubules of kidney and is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen.

Dapagliflozin does not inhibit other glucose transporters (present the in peripheral tissues) and is > 1,400 times more selective for SGLT2 than SGLT1 (the major transporter in the gut responsible for glucose absorption).

Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose and it continuous over the 24-hour dosing interval. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and eGFR. Thus, in subjects with normal blood glucose and/or low eGFR, dapagliflozin has a low propensity to cause hypoglycaemia, as the amount of filtrated glucose is small and can be reabsorbed by SGLT1 and unblocked SGLT2 transporters. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia.

Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which increases tubuloglomerular feedback and reduce intraglomerular pressure. This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling and preserve

renal function. The cardiac and renal benefits of dapagliflozin are not solely dependent on the blood glucose-lowering effect and not limited to patients with diabetes.

Metformin

Metformin is a biguanide class of oral antidiabetic drugs. Metformin produces its antihyperglycemic effects via following 3 mechanisms:

1. Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
2. In muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation.
3. Delay of intestinal glucose absorption.

5.2Pharmacodynamic Properties

Dapagliflozin

Following the oral administration of dapagliflozin in patients with type 2 diabetes mellitus, increase in the amount of glucose excreted in the urine was observed. Dapagliflozin doses of 5 mg or 10 mg per day in patients with type 2 diabetes mellitus for 12 weeks resulted in excretion of approximately 70 grams of glucose in the urine per day at week 12. Evidence of sustained glucose excretion was seen in subjects with type 2 diabetes mellitus when dapagliflozin 10 mg per day was given for up to 2 years. After discontinuation of dapagliflozin 10 mg per day dose, on average, the elevation in urinary glucose excretion appears to be normal in 3 days.

This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume in subjects with type 2 diabetes mellitus. Urinary volume increases in subjects with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and amounted to approximately 375 ml/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.

Dapagliflozin acts independently of insulin secretion and insulin action. Improvement in homeostasis model assessment for beta cell function (HOMA-β) has been observed in clinical studies with dapagliflozin.

Metformin

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

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT). In clinical studies, the major non-glycemic effect of metformin is either weight neutral or modest weight loss.

5.3Pharmacokinetic Properties

Dapagliflozin

Absorption: Dapagliflozin is rapidly and well absorbed after oral administration. Following oral use, the maximum plasma concentration (C_{max}) reached within 2 hours under fasting state. The C_{max} and AUC values increase dose proportionally with increase in dapagliflozin dose in the therapeutic dose

range. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%.

Effect of food/meal: Administration of dapagliflozin with a high-fat meal decreases its C_{max} by up to 50% and prolongs T_{max} by approximately 1 hour, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful. Thus, dapagliflozin can be administered with or without food.

Distribution: Plasma protein binding of dapagliflozin is approximately 91% and it does not alter in patients with renal or hepatic impairment. The mean steady-state volume of distribution of dapagliflozin is 118 liters.

Metabolism: Dapagliflozin is extensively metabolized, primarily to dapagliflozin 3-O-glucuronide, which is an inactive metabolite. The metabolism of dapagliflozin is primarily mediated by UGT1A9 (an enzyme present in the liver and kidney); CYP-mediated metabolism is a minor clearance pathway in humans.

Excretion: Dapagliflozin and its metabolites are primarily excreted via the renal pathway with less than 2% as unchanged dapagliflozin. Following a single 50 mg dose of [^{14}C]-dapagliflozin (radioactive), 75% and 21% of administered dose is excreted in urine and feces, respectively. In feces, approximately 15% of the dose is excreted as active (unchanged) drug. The mean terminal half-life (t½) of dapagliflozin is approximately 12.9 hours following a single oral dose of 10 mg in healthy subjects.

Metformin Sustained Release

Absorption: After an oral dose of the sustained release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a T_{max} at 7 hours (T_{max} for the immediate release tablet is 2.5 hours). The AUC after a single oral administration of 2000 mg of metformin sustained release tablets is similar to that observed after administration of 1000 mg of metformin immediate release tablets twice daily. The extent of absorption (as measured by AUC) of metformin (in sustained release form) increases when given with food. There was no effect of food on C_{max} and T_{max} of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of metformin in sustained release form.

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 volume of distribution ranged between 63 to 276 liters.

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

Excretion: 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 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.

6. Nonclinical Properties

Dapagliflozin

6.1 Animal Toxicology

Carcinogenesis: Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in 2-year carcinogenicity studies. Oral doses in mice consisted of 5, 15, and 40 mg/kg/day in males and 2, 10, and 20 mg/kg/day in females, and oral doses in rats were 0.5, 2, and 10 mg/kg/day for both males and females. The highest doses evaluated in mice were approximately 72-times (males) and 105-times (females) the clinical dose of 10 mg per day, based on AUC exposure. In rats, the highest dose was approximately 131-times (males) and 186-times (females) the clinical dose of 10 mg per day, based on AUC exposure.

Mutagenesis: Dapagliflozin was negative in the Ames mutagenicity assay and was positive in a series of *in vitro* clastogenicity assays in the presence of S9 activation and at concentrations greater than or equal to 100 μg/ml. Dapagliflozin was negative for clastogenicity in a series of *in vivo* studies evaluating micronuclei or DNA repair in rats at exposure multiples greater than 2100-times the clinical dose.

There was no carcinogenicity or mutagenicity signal in animal studies, suggesting that dapagliflozin does not represent a genotoxic risk to humans.

Impairment of Fertility: Dapagliflozin had no effects on mating, fertility, or early embryonic development in treated male or female rats at exposure multiples less than or equal to 1708-times and 998-times the maximum recommended human dose in males and females, respectively.

Metformin

Carcinogenesis: Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 3 times the maximum recommended human daily dose of 2550 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

Mutagenesis: There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Impairment of 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 2 times the maximum recommended human daily dose of 2550 mg based on body surface area comparisons.

Teratogenicity: Metformin hydrochloride did not adversely affect development outcomes when administered to pregnant rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 5 times a 2550 mg clinical dose based on body surface area comparisons for rats and rabbits, respectively.

7. Description

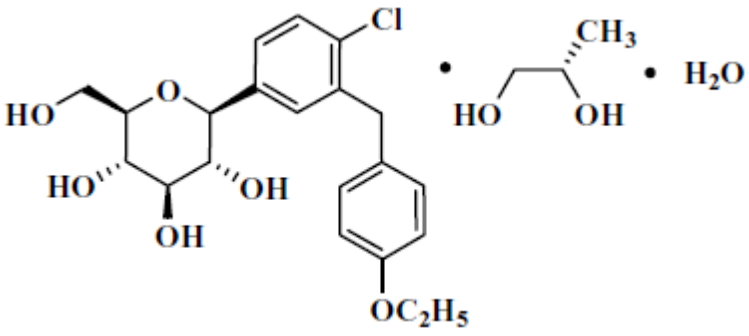
DIABIZ-M Tablets are one side pink to light pink colour and other side white to off white colour bilayered, elongated, biconvex film coated tablets plain on both sides.

DIABIZ-M Forte Tablets are one side yellow to light yellow coloured and other side white to off white coloured, bilayered, elongated, biconvex film coated tablets scored on one side.

Dapagliflozin

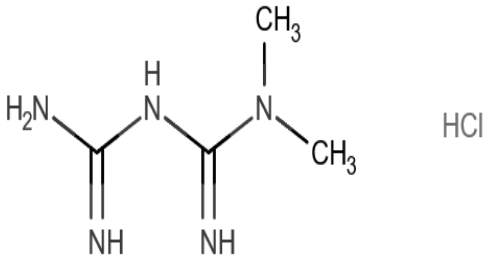
Dapagliflozin propanediol is the propanediol form of dapagliflozin, a selective sodium-glucose co-transporter subtype 2 (SGLT2) inhibitor with antihyperglycemic activity. Dapagliflozin propanediol monohydrate is a hydrate that consists of dapagliflozin compounded with (S)-propylene glycol and hydrate in a (1:1:1) ratio.

Dapagliflozin propanediol occurs as a white to off-white non-hygroscopic powder.
Molecular Weight: 502.98 g/mol.
Molecular Formula: C21H25ClO6•C3H8O2•H2O.
Chemical Name: (2S,3R,4R,5S,6R)-2-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol;(2S)-propane-1,2-diol;hydrate (1:1:1).
Structural Formula:



Metformin Hydrochloride

Metformin hydrochloride is the hydrochloride salt of the biguanide metformin with antihyperglycemic effect.
Metformin hydrochloride is white powder which is freely soluble in water and slightly soluble in alcohol.
Molecular Weight: 165.62 g/mol.
Molecular Formula: C4H12ClN5.
Chemical Name: 3-(diaminomethylidene)-1,1-dimethylguanidine;hydrochloride.
Structural Formula:



Inactive ingredients (excipients) of DIABIZ-M Tablet contain Lactose Monohydrate, Microcrystalline Cellulose, Crospovidone, Polyvinylpyrrolidone, Colour Erythrosine Lake, Colloidal Silicon Dioxide, Hydroxypropyl Methylcellulose, Diethyl phthalate, Titanium Dioxide, Hydroxy Propyl Cellulose, Xanthan Gum, Ethyl Cellulose, Talcum, and Magnesium Stearate.

Inactive ingredients (excipients) of DIABIZ-M Forte Tablet contain Lactose Monohydrate, Microcrystalline Cellulose, Crospovidone, Polyvinylpyrrolidone, Colour Yellow Oxide of Iron, Colloidal Silicon Dioxide, Hydroxypropyl Methylcellulose, Diethyl phthalate, Titanium Dioxide, Hydroxy Propyl Cellulose, Ethyl Cellulose, Xanthan Gum, Starch, Talcum, and Magnesium Stearate.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

18 months

8.3Packaging Information

15 tablets per strip.

8.4Storage and Handling Instructions

Store protected from light and moisture at a temperature not exceeding 30°C.
Keep out of reach of children.

9. Patient Counseling Information

Instructions to Patients

- Patients should be advised to take this medicine as an adjuvant to diet and exercise to improve blood sugar levels. This drug therapy is not an alternative or substitute for diet and exercises; thus, patients should continue to follow a good lifestyle.
- Instruct patients to take this medicine exactly as prescribed by physician. Do not change the dose or stop therapy without consulting doctor.
- Patients are advised to take DIABIZ-M/DIABIZ-M Forte Tablets once a day, with or without food. It may be easier to take your dose if you do it at the same time every day, such as with breakfast or dinner, or at bedtime. Do not take more than one dose at a time.

- If patients miss a dose, they can take it as soon as they remember. Do not take this medicine if it has been more than 12 hours since the last missed dose. Wait and take the next dose at regular scheduled time.
- Instruct patients not to take this medicine if they have severe liver and/or kidney dysfunction.
- Patients are advised not to take this medicine for type 1 diabetes or for the treatment of diabetic ketoacidosis.
- Instruct patients not to use this medicine during severe infection, surgery, trauma, or if they are seriously dehydrated.
- Advise patients to use this medicine with caution if they have history of abdominal surgery or intestinal obstruction.
- Instruct patients not to take this medicine if they are going to have a contrast x-ray.
- Advise patients not to drink alcohol excessively while on this drug therapy.
- Pregnant women should strictly avoid use of this medicine. When pregnancy is detected or planned, discontinue DIABIZ/DIABIZ-M Tablets as soon as possible.
- Advise nursing women not to breastfeed during treatment with DIABIZ-M/DIABIZ-M Tablets.
- Patients should be informed that while taking DIABIZ-M/DIABIZ-M Forte Tablets do not stop taking other prescription medicines, including other anti-diabetic medicines, without consulting their doctor.
- Inform patients that serious hypersensitivity reactions (e.g., urticaria, anaphylactic reactions, and angioedema) have been reported with dapagliflozin. Advise patients to immediately report any signs or symptoms suggesting these reactions and stop taking this medicine immediately.
- Patients should be informed that this medicine may cause dehydration (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension). Risk of dehydration is higher if you take this medicine along with diuretics or if your age is above 65 years or if you are on a low salt diet or if you have kidney problems.

10. Details of Manufacturer

Synokem Pharmaceuticals Ltd.
Plot No.56-57, Sector-6A, I.I.E (SIDCUL)
Ranipur (BHEL), Haridwar – 249 403
(Uttarakhand)

11. Details of Permission or License Number with Date

Mfg. Lic. No. : 27/UA/2018 Date of FDA Product Permission: 08/07/2021

12. Date of Revision

September 2021.

Marketed by:
BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.