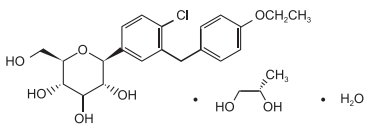
Dafo™ M

ڈیفو ایم

(Dapagliflozin+Metformin HCl)

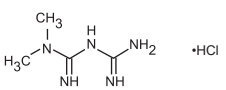
Film-coated Tablets 5mg + 850mg and 5mg + 1000mg

DESCRIPTION
Dafo M (Dapagliflozin + Metformin HCl) contains two oral anti-hyperglycemic medications used in the management of type 2 diabetes: Dapagliflozin and Metformin HCl.
Dapagliflozin is a highly potent, selective and reversible inhibitor of SGLT2. Chemically, Dapagliflozin is D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl) methyl] phenyl]-, (1S)-, compounded with (2S)-1,2-propanediol, hydrate (1:1:1). Its molecular formula is $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$ and the structural formula is:



Dapagliflozin Propanediol Monohydrate

Metformin HCl (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral anti-hyperglycemic agents. It has a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and the structural formula is:



Metformin HCl

QUALITATIVE AND QUANTITATIVE COMPOSITION
Dafo M (Dapagliflozin + Metformin HCl) is available for oral administration as:

Dafo M Tablets 5mg + 850mg
Each film-coated tablet contains:
Dapagliflozin Propanediol Monohydrate equivalent to Dapagliflozin…5mg
Metformin HCl USP…850mg

Dafo M Tablets 5mg + 1000mg
Each film-coated tablet contains:
Dapagliflozin Propanediol Monohydrate equivalent to Dapagliflozin…5mg
Metformin HCl USP…1000mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Dapagliflozin
Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, Dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion. Dapagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to, lowering both pre- and afterload of the heart and downregulation of sympathetic activity and decreased intraglomerular pressure which is believed to be mediated by increased tubuloglomerular feedback.

Metformin HCl
It is a biguanide with anti-hyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia. Metformin HCl stimulates intracellular glycogen synthesis by acting on glycogen synthase.
Metformin HCl may active via three mechanisms;
- By reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
- In muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilization.
- By delaying intestinal glucose absorption.

Pharmacokinetics
Absorption
Dapagliflozin
After oral administration, Dapagliflozin is rapidly absorbed with maximum plasma concentrations (C_{max}) usually attained within 2 hours after administration in the fasted state. Geometric mean steady-state Dapagliflozin C_{max} and AUC_τ values following once daily 10mg doses of Dapagliflozin were 158 ng/mL and 628 ng h/mL, respectively. The absolute oral bioavailability of Dapagliflozin following the administration of a 10mg dose is 78%.

Metformin HCl
After an oral dose of Metformin HCl, t_{max} is reached in 2.5 h. Absolute bioavailability of a 500mg or 850mg Metformin HCl tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in feces was 20-30%.
After oral administration, Metformin HCl absorption is saturable and incomplete. It is assumed that the pharmacokinetics of Metformin HCl absorption is non-linear. At the usual Metformin HCl doses and dosing schedules, steady-state plasma concentrations are reached within 24-48 hours and are generally less than 1µg/mL.

Distribution
Dapagliflozin
Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g. renal or hepatic impairment). The mean steady-state volume of distribution of Dapagliflozin was 118 litres.

Metformin HCl
Metformin HCl is negligibly bound to plasma proteins. Metformin HCl 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 V_d *ranged between 63-276 l.*

Metabolism
Dapagliflozin
Dapagliflozin is extensively metabolised, primarily to yield Dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of Dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP-mediated metabolism was a minor clearance pathway in humans.

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

Elimination
Dapagliflozin
The mean plasma terminal half-life ($t_{1/2}$) for Dapagliflozin was 12.9 hours following a single oral dose of Dapagliflozin 10mg to healthy subjects. The mean total systemic clearance of Dapagliflozin administered intravenously was 207 mL/min. Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2% as unchanged Dapagliflozin. After administration of a 50mg [14C]-Dapagliflozin dose, 96% was recovered, 75% in urine and 21% in feces. In feces, approximately 15% of the dose was excreted as parent drug.

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

Special population
Patients with renal impairment
Dapagliflozin
At steady-state (20mg once-daily Dapagliflozin for 7 days), subjects with type 2 diabetes mellitus and mild, moderate or severe renal impairment (as determined by iohexol plasma clearance) had mean systemic exposures of Dapagliflozin of 32%, 60% and 87% higher, respectively, than those of subjects with type 2 diabetes mellitus and normal renal function. The steady-state 24-hour urinary glucose excretion was highly dependent on renal function and 85, 52, 18 and 11 g of glucose/day was excreted by subjects with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. The impact of hemodialysis on Dapagliflozin exposure is not known.

Metformin HCl
In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of Metformin HCl is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance, leading to increased levels of Metformin HCl in plasma.

Patients with hepatic impairment
Dapagliflozin
In subjects with mild or moderate hepatic impairment (Child-Pugh classes A and B), mean C_{max} and AUC of Dapagliflozin were up to 12% and 36% higher, respectively, compared with healthy matched control subjects. These differences were not considered to be clinically meaningful. In subjects with severe hepatic impairment (Child-Pugh class C) mean C_{max} and AUC of Dapagliflozin were 40% and 67% higher than matched healthy controls, respectively.

Metformin HCl
No pharmacokinetic studies of Metformin HCl have been conducted in subjects with hepatic impairment.

THERAPEUTIC INDICATIONS
Dafo M (Dapagliflozin + Metformin HCl) is indicated in adults for the treatment of type 2 diabetes mellitus as an adjunct to diet and exercise:
- In patients insufficiently controlled on their maximally tolerated dose of Metformin HCl alone.
- In combination with other medicinal products for the treatment of diabetes in patients insufficiently controlled with Metformin HCl and these medicinal products.
- In patients already being treated with the combination of Dapagliflozin and Metformin HCl as separate tablets.

DOSAGE AND ADMINISTRATION
Adults with normal renal function (glomerular filtration rate [GFR] ≥ 90mL/min)
The recommended dose of Dafo M (Dapagliflozin + Metformin HCl) is one tablet twice daily.

For patients insufficiently controlled on Metformin HCl monotherapy or Metformin HCl in combination with other medicinal products for the treatment of diabetes
Patients insufficiently controlled on Metformin HCl alone or in combination with other medicinal products for the treatment of diabetes should receive a total daily dose of Dafo M (Dapagliflozin + Metformin HCl) equivalent to Dapagliflozin 10mg, plus the total daily dose of Metformin HCl, or the nearest therapeutically appropriate dose, already being taken. When Dafo M (Dapagliflozin + Metformin HCl) is used in combination with insulin or an insulin secretagogue such as sulphonylurea, a lower dose of insulin or sulphonylurea may be considered to reduce the risk of hypoglycemia.

Patients switching from separate tablets of Dapagliflozin and Metformin HCl
Patients switching from separate tablets of Dapagliflozin (10mg total daily dose) and Metformin HCl to Dafo M (Dapagliflozin + Metformin HCl), should receive the same daily dose of Dapagliflozin and Metformin HCl already being taken or the nearest therapeutically appropriate dose of Metformin HCl.

Special Population
Patients with renal impairment
A GFR should be assessed before initiation of treatment with Metformin HCl 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.
The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the riskof lactic acidosis should be reviewed before considering initiation of metformin in patients with GFR < 60mL/min.
If no adequate strength of Dafo M (Dapagliflozin + Metformin HCl) is available, individual mono-components should be used instead of the fixed dose combination.

Table 1. Dosage in patients with renal impairment

GFR mL/min	Metformin HCl	Dapagliflozin
60-89	Maximum daily dose is 3000mg. Dose reduction may be considered in relation to declining renal function.	Maximum total daily dose is 10mg.
45-59	Maximum daily dose is 2000mg. The starting dose is at most half of the maximum dose.	Dapagliflozin should not be initiated. Maximum total daily dose is 10mg.
30-44	Maximum daily dose is 1000mg. The starting dose is at most half of the maximum dose.	Dapagliflozin is not recommended.
< 30	Metformin is contraindicated.	Dapagliflozin is not recommended.

Patients with hepatic impairment
Dafo M (Dapagliflozin + Metformin HCl) must not be used in patients with hepatic impairment.

Elderly
Dafo M (Dapagliflozin + Metformin HCl) should be used with caution in elderly patients. Monitoring of renal function is necessary to aid in prevention of Metformin HCl-associated lactic acidosis, particularly in elderly patients. Risk of volume depletion with Dapagliflozin should also be taken into account.

Pediatric population
The safety and efficacy of Dafo M (Dapagliflozin + Metformin HCl) in children and adolescents aged 0 to <18 years have not yet been established.

Method of administration
Dafo M (Dapagliflozin + Metformin HCl) should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with Metformin HCl.

CONTRAINDICATIONS
The combination of Dapagliflozin and Metformin HCl is contraindicated in patients with:
- Hypersensitivity to Dapagliflozin, Metformin HCl or to any of the excipient of the product.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).
- Severe renal failure (eGFR below 30mL/min).
- Diabetic pre-coma.
- Acute conditions with the potential to alter renal function such as dehydration, severe infection, shock.
- Acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, shock.
- Hepatic impairment, acute alcohol intoxication, alcoholism.

ADVERSE REACTIONS
Very Common: Hypoglycemia (when used with sulphonylurea or insulin) and gastrointestinal symptoms.

Common: Vulvovaginitis, balanitis and related genital infections, urinary tract infection, taste disturbance, dizziness, rash, back pain, dysuria, polyuria, haematocrit increased, creatinine renal clearance decreased during initial treatment, vitamin B_{12} deficiency and dyslipidaemia.

Uncommon: Fungal infection, volume depletion, thirst, constipation, dry mouth, nocturia, vulvovaginal pruritus, pruritis genital, blood creatinine increased during initial treatment, blood urea increased and weight decreased.

Rare: Diabetic ketoacidosis.

Very Rare: Fournier's gangrene, lactic acidosis, liver function disorders, hepatitis, urticaria, erythema and pruritus.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

PRECAUTIONS

LACTIC ACIDOSIS

Postmarketing cases of Metformin HCl-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and Metformin HCl plasma levels generally >5mcg/mL.
Risk factors include renal impairment, concomitant use of certain drugs, age >65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage Metformin HCl-associated lactic acidosis in these high-risk groups.
If lactic acidosis is suspected, discontinue Dapagliflozin + Metformin HCl and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

Lactic Acidosis
Lactic acidosis is a very rare but serious metabolic complication, mostly occurs due to acute worsening of renal function or cardiorespiratory illness or sepsis. Dapagliflozin + Metformin HCl accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. In case of dehydration (severe diarrhea or vomiting, fever or reduced fluid intake), Dapagliflozin + Metformin HCl should be temporarily discontinued. Medicines that can acutely impair renal function (such as antihypertensive, diuretics and NSAIDs) should be initiated with caution in Metformin HCl-treated patients.

General
Dapagliflozin + Metformin HCl should not be used in patients with type 1 diabetes.

Use in patients at risk for volume depletion and/or hypotension
Caution should be exercised in patients for whom a Dapagliflozin-induced drop in blood pressure could pose a risk, such as patients on anti-hypertensive therapy with a history of hypotension or elderly patients.

Diabetic ketoacidosis
The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.
In patients where diabetic ketoacidosis is suspected or diagnosed, treatment with Dapagliflozin should be discontinued immediately. Treatment should be interrupted in patients who are hospitalized for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with Dapagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilized. Before initiating Dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.

Necrotising fasciitis of the perineum (Fournier's gangrene)
Post marketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors. Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. If Fournier's gangrene is suspected, Dapagliflozin + Metformin HCl should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Urinary tract infections
Urinary glucose excretion may be associated with an increased risk of urinary tract infection. Therefore, temporary interruption of treatment should be considered when treating pyelonephritis or urosepsis.

Elderly (≥ 65 years)
Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics.
Elderly patients are more likely to have impaired renal function, and/or to be treated with anti-hypertensive medicinalproducts that may cause changes in renal function such as angiotensin-converting enzyme inhibitors (ACE-I) andangiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to elderly patients as to all patients.

Lower limb amputations
An increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term, clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot care.

Urine laboratory assessments
Due to its mechanism of action, patients taking this medicinal product will test positive for glucose in their urine.

Renal function
The glycaemic efficacy of Dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and is likely absent in patients with severe renal impairment. Dapagliflozin + Metformin HCl should not be initiated inpatients with GFR < 60mL/min and should be discontinued at GFR persistently below 45mL/min.
Renal function should be assessed:
- Before initiation of treatment and regularly thereafter.
- For renal function with GFR levels < 60mL/min and in elderly patients, at least 2 to 4 times per year.
- Prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter.
- If renal function falls persistently below GFR 45mL/min, treatment should be discontinued.
- Metformin HCl is contraindicated in patients with GFR of < 30mL/min and should be temporarily discontinued in the presenceof conditions that alter renal function.

Administration of iodinated contrast agent
Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metforminaccumulation and increased risk of lactic acidosis. Dapagliflozin + Metformin HCl should be discontinued prior to, or at the time of, the imagingprocedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

Increased haematocrit
Increased haematocrit has been observed with Dapagliflozin treatment. Patients with pronounce delevations in haematocrit should be monitored and investigated for underlying haematological disease.

Change in clinical status of patients with previously controlled type 2 diabetes
As this medicinal product contains Metformin HCl, a patient with type 2 diabetes previously well-controlled on it who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and Metformin HCl levels. If acidosis of either form occurs, treatment must be stopped immediately and other appropriate corrective measures initiated.

Vitamin B_{12} decrease/deficiency
Metformin HCl may reduce vitamin B_{12} serum levels. In case of suspicion of vitamin B_{12} deficiency (such as anaemia or neuropathy), vitamin B_{12} serum levels should be monitored. Periodic vitamin B_{12} monitoring could be necessary in patients with risk factors for vitamin B_{12} deficiency.

Surgery
Dapagliflozin + Metformin HCl must be discontinued at the time of surgery with general, spinal or epidural anesthesia. 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.

Patients with known or suspected mitochondrial diseases
In patients with known mitochondrial diseases such as Mitochondrial Encephalomyopathy with Lactic Acidosis, and Stroke-like episodes (MELAS) syndrome and Maternally Inherited Diabetes and Deafness (MIDD), Metformin HCl is not recommendeddue to the risk of lactic acidosis exacerbation and neurologic complications which may lead to worsening of the disease.
In case of signs and symptoms suggestive of MELAS syndrome or MIDD after the intake of Metformin HCl, treatment with Metformin HCl should be withdrawn immediately and prompt diagnostic evaluation should be performed.

Effects on ability to drive and use machines
Dapagliflozin + Metformin HCl has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycemia when this medicinal product is used in combination with other glucose-lowering medicinal products known to cause hypoglycemia.

Pregnancy
The use of this medicinal product is not recommended during the second and third trimesters of pregnancy. When pregnancy is detected, treatment with Dapagliflozin + Metformin HCl should be discontinued.

Nursing Mothers
Metformin HCl is excreted into human breast milk. It is unknown whether Dapagliflozin is excreted in human milk. Dapagliflozin + Metformin HCl should not be administered during nursing.

DRUG INTERACTIONS
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.

Diuretics
This medicinal product may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

Insulin or Insulin Secretagogues
Insulin and insulin secretagogues such as sulphonylureas, cause hypoglycemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with Dapagliflozin + Metformin HCl.

Drugs that Reduce Metformin HCl Clearance
Cationic substances that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with Metformin HCl by competing for common renal tubular transport systems. Therefore, close monitoring of glycemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are coadministered.

Alcohol
Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in the case of fasting, malnutrition or hepatic impairment due to the Metformin HCl active substance of this medicinal product. Consumption of alcohol and medicinal products containing alcohol should be avoided.

NSAIDs, ACE Inhibitors, angiotensin II receptor antagonists and diuretics
These medicinal products can adversely affect renal function which may increase the risk of lactic acidosis when given in combination with Metformin HCl. Therefore, close monitoring of renal function is necessary.

Glucocorticoids beta-2-agonists and diuretics
Glucocorticoids, beta-2 agonists and diuretics have intrinsic hyperglycemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment with such medicinal products. If necessary, the dose of the anti-hyperglycemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

OVERDOSAGE
Dapagliflozin
Single doses of up to 500mg Dapagliflozin (equivalent to 50-times the maximum recommended human dose) did not show any toxicity. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

Metformin HCl
High overdose or concomitant risks of Metformin-HCl may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital.

STORAGE
Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Dafo M (Dapagliflozin + Metformin HCl) Tablets 5mg + 850mg are available in pack of 14's.
Dafo M (Dapagliflozin + Metformin HCl) Tablets 5mg + 1000mg are available in pack of 14's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

Getz pharma (PVT) LIMITED
www.getzpharma.com
29-30/27, K.I.A., Karachi, Pakistan

200023376