UNISON PHARMACEUTICALS PVT. LTD.

ART WORK APPROVAL FORM

Product Name: DGSON-M 1000	Market: Francophone	Mfg. Location: Unit-3

DGSON-M 1000

DGSON-M 1000

Utilisation de cette notice réservée aux professionnels de santé homologués, hôpitaux, laboratoires ou utilisateurs du produit

Notice : Information de l'utilisateur

DGSON-M 1000

DGSON-M 1000

Dapagliflozine et Chlorhydrate de Metformine 5mg / 1000mg comprimés pelliculés

Chaque comprimé pelliculé contient :

Dapagliflozine Propanediol de Monohydraté

Equivalent à Dapagliflozine 5 mg

Chlorhydrate de Metformine Ph. Eur. 1000 mg

Excipients q.s.

Couleur : Dioxyde de titane Ph. Eur. (E171), Oxyde de fer jaune (E172).

Liste des excipients

Forme pharmaceutique

Pharmacodynamique

Indication

Posologie et mode d'administration

Contre-indications

Mise en garde spéciales et précautions d'emploi

Interactions avec d'autres médicaments et autres formes d'interactions

Fertilité, Grossesse et Allaitement

Effets sur l'aptitude à conduire des véhicules et à utiliser des machines

Effets indésirables

Surdosage

Présentation

Précautions particulières de conservation

Conditions de prescription et de délivrance

Liste-I

Laboratoire Titulaire d'AMM et Fabricant / Marketing Authorization Holder and Manufacturer :

UNISON PHARMACEUTICALS PVT. LTD.

Unit-III, C-7,8,9, Steel Town, Opp. Nova Petro, Moraiya, Ta.- Sanand, Dist.: Ahmedabad-382213, Gujarat, India.

Date de dernière révision du texte: Septembre-2024

650 mm

Size: 650 x 290 mm

Colour: P P Black C

Pharmacode: 856

290 mm

French

Do not print Outline

Font Type: Arial
Font Size: 6 pt
Brand Font Size: 7 pt

DATE: 01/10/2024 VERSION:01

INSERT/PIL/OUTSERT SPECIFICATION

Artwork Code	02 222 1885 00	Open Size	650 x 290 mm	Close Size	30 x 51 mm	Floding Condition	Folded
Type of Paper	Bible	GSM of Paper	40 gsm	Colour of Paper	White	Colour of Matter	P P Black C
Pharmacode	856	Any other special process	N.A.	Old Artwork Code	N.A.	Old Pharmacode	N.A.
Reference Change Control no.	N.A.	of Plant	N.A.				

Review & Approved By Contract Giver/Customer/Authority/MA Holder (If Applicable) :

Sign & Date :

Name :

Designation :

Department :

ARTWORK APPROVAL FORM

Product Name: DGSON-M 1000 | **Market:** Francophone | **Mfg. Location:** Unit-3

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Notice: User information
DGSON-M 1000

DGSON-M 1000
Dapagliflozin and Metformin Hydrochloride 5mg / 1000mg Film-Coated Tablets
Each film coated tablet contains:
Dapagliflozin Propanediol Monohydrate
Eq. to Dapagliflozin 5 mg
Metformin Hydrochloride Ph. Eur. 1000 mg
Excipients q.s.
Colour: Iron Oxide Yellow (E172), Titanium Dioxide Ph. Eur. (E171)

List of excipients
Microcrystalline Cellulose, Povidone K-90, Sodium Starch Glycolate, Zinc Stearate, Opadry II Yellow (85F520441), Purified Water

Product description: Yellow, biconvex, oval, film-coated tablets engraved with "5"1000" on one side and plain on the other side.
Chemical name (Dapagliflozin Propanediol Monohydrate): (2S,3R,4R,5S,6R)-2-(3-(4-Ethoxybenzyl)-4-chlorophenyl)-6-hydroxymethyl-tetrahydro-2H-pyran-3,4,5-triol propane-1,3-diol monohydrate; *Molecular formula:* $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$; *Molecular weight:* 502.96 gm/mol.
Chemical name (Metformin Hydrochloride EP): 1,1-Dimethylbiguanide hydrochloride; *Molecular formula:* $C_4H_{11}N_5 \cdot HCl$; *Molecular weight:* 165.62 gm/mol.

Pharmacodynamics
Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs; **ATC code:** A10BD15
Mechanism of action
DGSON-M 1000 combines two anti-hyperglycaemic medicinal products with different and complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: dapagliflozin, a SGLT2 inhibitor, and metformin hydrochloride, a member of the biguanide class.

Dapagliflozin
Dapagliflozin is a highly potent (K$_i$: 0.55 nM), selective and reversible inhibitor of SGLT2. 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 improves peripheral glucose uptake and utilisation in muscle; by delaying intestinal glucose absorption.
Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

Pharmacodynamic effects
Dapagliflozin
Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in subjects with type 2 diabetes mellitus following the administration of dapagliflozin. Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in subjects with type 2 diabetes mellitus for 12 weeks. Evidence of sustained glucose excretion was seen in subjects with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years.
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
Dapagliflozin was administered to approximately 375 mL/day. The increase in type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and amount of approximately 375 mL/day. The increase in urine volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.
Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a sustained reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from -48.3 to -18.3 micromoles/L (-0.871 to -0.33 mg/dL).
The pharmacodynamics of 5 mg dapagliflozin twice daily and 10 mg dapagliflozin once daily were compared in healthy subjects. Administration of 5 mg dapagliflozin twice daily gave similar overall exposures (AUC$_{τ}$) over a 24-hour period as 10 mg dapagliflozin administered once daily. At a dapagliflozin 5 mg administered twice daily compared with 10 mg dapagliflozin once daily resulted in lower peak dapagliflozin plasma concentrations (C_{max}) and higher trough plasma dapagliflozin concentrations ($C_{τ}$).

Interaction with food
The administration of this medicinal product in healthy volunteers after a high fat meal compared to after the fasted state resulted in the same extent of exposure for both dapagliflozin and metformin. The meal resulted in a delay of 1 to 2 hours in the peak concentrations and a decrease in the maximum plasma concentration of 29% of dapagliflozin and 17% of metformin. These changes are not considered to be clinically meaningful.

Paediatric population
Pharmacokinetics in the paediatric population have not been studied.
The following statements reflect the pharmacokinetic properties of the individual active substances of this medicinal product.

Dapagliflozin
Absorption
Dapagliflozin was rapidly and well absorbed after oral administration. Maximum dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. Geometric mean steady-state dapagliflozin Cmax and AUC, values following dose daily 10 mg doses of dapagliflozin were 158 ng/mL and 628 ng h/mL, respectively. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%.
Distribution
Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g. renalor hepatic impairment). The mean steady-state volume of distribution was 118 liters.
Biotransformation
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, which was present in the liver and kidney, and CYP-mediated metabolism was a minor clearance pathway in humans.
Elimination
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 following 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 50 mg [14C]-dapagliflozin dose, 96% was recovered, 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose was excreted as parent drug.
Linearity
Dapagliflozin exposure increased proportional to the increment in dapagliflozin dose over the range of 0.1 to 500 mg and its pharmacokinetics did not change with time upon repeated daily dosing for up to 24 weeks.
Special populations
Renal impairment
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 to healthy matched control subjects. These differences were not considered to be clinically meaningful. In subjects with severe hepatic impairment (Child-Pugh class C) mean Cmax and AUC of dapagliflozin were 40% and 67% higher than matched healthy controls, respectively.
Elderly (≥ 65 years)
There is no clinically meaningful increase in exposure based on age alone in subjects up to 70 years old. However, an increased exposure due to age-related decrease in renal function can be expected. There are insufficient data to draw conclusions regarding exposure in patients > 70 years old.
Paediatric population
Pharmacokinetics and pharmacodynamics (glucosuria) in children with type 2 diabetes mellitus aged 10-17 years were similar to those observed in adults with type 2 diabetes mellitus.
Gender
The mean dapagliflozin AUC$_{τ}$ in females was estimated to be about 22% higher than in males.
Race
There were no clinically relevant differences in systemic exposures between White, Black or Asian races.
Body weight
Dapagliflozin exposure was found to decrease with increased weight. Consequently, low-weight patients may have somewhat increased exposure and patients with high weight somewhat decreased exposure. However, the differences in exposure were not considered clinically meaningful.
Paediatric population
Pharmacokinetics and pharmacodynamics (glucosuria) in children with type 2 diabetes mellitus aged 10-17 years were similar to those observed in adults with type 2 diabetes mellitus.

Metformin
Absorption
After a oral dose of metformin, tmax is reached in 2.5h. Absolute bioavailability of a 500 mg or 850 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady-state plasma concentrations are reached within 24-48 hours and are generally less than 1 µg/mL. In controlled clinical trials, maximum metformin plasma levels (Cmax) did not exceed 5 µg/mL, even at maximum doses.

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 63-276L.

Biotransformation
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.

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

Indication
DGSON-M 1000 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 alone
- in combination with other medicinal products for the treatment of diabetes in patients insufficiently controlled with metformin and these medicinal products

For results seen in studies already being treated with the combination of dapagliflozin and metformin as separate tablets.
For study results with respect to combination of therapies, effects on glycaemic control and cardiovascular events, and the populations studied.
Posology and method of administration
Posology
Adults with normal renal function (glomerular filtration rate [GFR] ≥ 90 mL/min)
The recommended dose is one tablet twice daily. Each tablet contains a fixed dose of dapagliflozin and metformin.

For patients insufficiently controlled on metformin monotherapy or metformin in combination with other medicinal products for the treatment of diabetes:
Patients insufficiently controlled on metformin alone or in combination with other medicinal products for the treatment of diabetes should receive a total daily dose of DGSON-M 1000 equivalent to dapagliflozin 10 mg, plus the total daily dose of metformin, or the closest therapeutically appropriate dose, already being taken. When DGSON-M 1000 is used in combination with insulin or an insulin secretagogue such as sulphonylurea, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia.

For patients switching from separate tablets of dapagliflozin and metformin
Patients switching from dapagliflozin (10 mg total daily dose) and metformin to DGSON-M 1000 should receive the same daily dose of dapagliflozin and metformin already being taken or the nearest therapeutically appropriate dose of metformin.

Special populations
Renal impairment
A GFR should be assessed before initiation of treatment with metformin containing medicinal products and at least annually thereafter. In patients at 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 preferable be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin in patients with GFR < 60 mL/min.
If no adequate strength of DGSON-M 1000 is available, individual mono-components should be used instead of the fixed dose combination.
Dosage in patients with renal impairment

GFR mL/min	Metformin	Dapagliflozin
60-89	Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.	Maximum daily dose is 10 mg.
45-59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 10 mg.
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 10 mg. The glucose lowering efficacy of dapagliflozin is reduced.
<30	Metformin is contraindicated.	Maximum daily dose is 10 mg. Due to limited experience, it is not recommended to initiate treatment with dapagliflozin in patients with GFR < 25 mL/min. The glucose lowering efficacy of dapagliflozin is likely absent.

Hepatic impairment
This medicinal product must not be used in patients with hepatic impairment.
Elderly (≥ 65 years)
Because metformin is eliminated in part by the kidney, and because elderly patients are more likely to have decreased renal function, this medicinal product should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in elderly patients.
Paediatric population
The safety and efficacy of DGSON-M 1000 in children and adolescents aged 0 to < 18 years have not yet been established. No data are available.
Method of administration
DGSON-M 1000 should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin.

Contraindication
DGSON-M 1000 is contraindicated in patients with:
- hypersensitivity to the active substances or to any of the excipients listed in section 6.1;
- any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis);
- diabetic pre-coma;
- severe renal failure (GFR < 30 mL/min);
- 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,
  - hepatic impairment;
- acute alcohol intoxication, alcoholism

Warnings and Precautions
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. When dapagliflozin/metformin accumulates 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), DGSON-M 1000 should be temporarily discontinued and contact with a health care professional is recommended.
Medicinal products that can adversely impair renal function (such as antihypertensives, diuretics and non-steroidal anti-inflammatory drugs [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 on 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 DGSON-M 1000 and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (<7.35), increased plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio.

Renal function
Since the glucose-lowering efficacy of dapagliflozin is dependent on renal function, and is reduced in patients with GFR < 45 mL/min and is likely absent in patients with severe renal impairment.
Metformin is excreted by the kidney, and moderate to severe renal insufficiency increases the risk of lactic acidosis. Renal function should be assessed before initiation of treatment and regularly thereafter. Metformin is contraindicated in patients with GFR < 30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function.
Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive or diuretic therapy or when starting treatment with a NSAID.

Use in patients at risk for volume depletion and/or hypotension
Due to its mechanism of action, dapagliflozin increases diuresis which may lead to the modest decrease in blood pressure observed in clinical studies. It may be more pronounced in patients with high blood glucose concentrations.
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.
In case of intercurrent conditions that may lead to volume depletion (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit and electrolytes) is recommended. Temporary interruption of treatment with this medicinal product is recommended for patients who develop volume depletion until the depletion is corrected.

Diabetic ketoacidosis
Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors, including dapagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL). It is not known if DKA is more likely to occur with higher doses of dapagliflozin.

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 DKA is suspected or diagnosed, treatment with dapagliflozin should be discontinued immediately.

Treatment should be interrupted in patients who are hospitalised 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 in patients with these conditions has stabilised.

Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.

Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g. type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients.

Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

The safety and efficacy of DGSON-M 1000 in patients with type 1 diabetes have not been established and DGSON-M 1000 should not be used for treatment of patients with type 1 diabetes. In type 1 diabetes mellitus studies, DKA was reported with common frequency.

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. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

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. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, DGSON-M 1000 should be discontinued and prompt treatment (including antibiotics and surgical débridement) 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 medicinal products that may cause changes in renal function such as angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB). The same recommendations apply to dapagliflozin as to elderly patients as to all patients.

Cardiac failure
Experience with dapagliflozin in NYHA class IV is limited.

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.
Administration of iodinated contrast agents
Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. DGSON-M 1000 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
DGSON-M 1000 must be discontinued at the time of surgery with 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.

Change in clinical status of patients with previously controlled type 2 diabetes
As this medicinal product contains dapagliflozin, 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 levels. If acidosis of either form occurs, treatment must be stopped immediately and other appropriate corrective measures initiated.

Vitamin B12 decrease/deficiency
Metformin may lead to a decrease in B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors for vitamin B12 deficiency. Before initiation of vitamin B12 deficiency (such as anaemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contraindicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

Interaction with other medicinal products and other forms of interaction
Coadministration of metformin and dapagliflozin and metformin does not meaningfully alter the pharmacokinetics of either dapagliflozin or metformin in healthy subjects.
No interaction studies have been performed for DGSON-M 1000. The following statements reflect the information available on the individual active substances.

Dapagliflozin
Pharmacodynamic interactions
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 and insulin secretagogues
Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, 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, this medicinal product is not expected to alter the metabolic clearance of coadministered medicinal products that are metabolised by these enzymes.

Effect of other medicinal products on dapagliflozin
Interaction studies conducted in healthy subjects, using mainly a single-dose design, suggest that the pharmacokinetics of dapagliflozin are not altered by pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.

Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolising enzymes) a 22% decrease in dapagliflozin plasma exposure (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 inducers (e.g. carbamazepine, phenytoin, phenobarbital) is not expected.

Following coadministration of dapagliflozin with mefenamic acid (an inhibitor of UGT1A9), a 55% increase in dapagliflozin exposure was seen, but with no impact on 24-hour urinary glucose excretion. No dose adjustment is recommended.

Effect of dapagliflozin on other medicinal products
In interaction studies conducted in healthy subjects, using mainly a single-dose design, dapagliflozin did not alter the pharmacokinetics of pioglitazone, sitagliptin, glimepiride, metformin, hydrochlorothiazide, bumetanide, valsartan, digoxin (a P-gp substrate) or warfarin (S-warfarin, a CYP2C9 substrate), or the anti-coagulatory effects of warfarin as measured by INR. 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 glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Use of alternative methods to monitor glycaemic control is advised.

Paediatric population
Interaction studies have only been performed in adults.

Metformin
Concomitant use not recommended
Cationic substances that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with metformin by competing for common renal tubular transport systems. A study conducted in seven normal healthy volunteers showed that cimetidine, administered as 400 mg twice daily, increase metformin systemic exposure (AUC) by 50% and Cmax by 81%. Therefore, close monitoring of glycaemic 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 potential for accumulation of this medicinal product. Consumption of alcohol and medicinal products containing alcohol should be avoided.

Iodinated contrast agents
Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. DGSON-M 1000 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.

Combination requiring precautions for use
Glucocorticoids (given by systemic and local routes), beta-2 agonists, and diuretics have intrinsic hyperglycaemic 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 glucose-lowering medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

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.

Insulin and insulin secretagogues
Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with metformin.

Fertility, Pregnancy and Breast-feeding
Pregnancy
There are no data from the use of DGSON-M 1000 or dapagliflozin in pregnant women. Studies in rats treated with dapagliflozin have shown toxicity to the developing kidney in the foetus at exposures corresponding to the second and third trimesters of human pregnancy (see section 5.3). Therefore, the use of this medicinal product is not recommended during the second and third trimesters of pregnancy. A limited amount of data from the use of metformin in pregnant women has not shown an increased risk of congenital abnormalities. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.
When the patient plans to become pregnant, and during pregnancy, it is recommended that diabetes is not treated with this medicinal product, but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the foetus associated with abnormal blood glucose levels.

Breast-feeding
It is unknown whether this medicinal product or dapagliflozin (and/or its metabolites) are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk, as well as pharmacologically-mediated effects in nursing offspring. Metformin is excreted in human milk in small amounts. A risk to the newborns/infants cannot be excluded.
This medicinal product should not be used while breast-feeding.

Fertility
The effect of this medicinal product or dapagliflozin on fertility in humans has not been studied. In male and female rats, dapagliflozin showed no effects on fertility at any dose tested. For metformin, studies in animals have not shown reproductive toxicity.

Effects on ability to drive and use machines
DGSON-M 1000 has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when this medicinal product is used in combination with other glucose-lowering medicinal products known to cause hypoglycaemia.

Undesirable effects
DGSON-M 1000 has been demonstrated to be bioequivalent with coadministered dapagliflozin and metformin. There have been no therapeutic clinical trials conducted with DGSON-M 1000.
Adverse reactions in dapagliflozin and metformin immediate-release clinical trial and post-marketing data

System organ class	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations		Vulvovaginitis, balanitis and related genital infections [a,c] Urinary tract infection [b,c]	Fungal infection		Necrotising fasciitis of the perineum (Fournier's gangrene)[c]
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)[c]	Vitamin B12 decrease/ deficiency[d]	Volume depletion[c,e] Thirst[e]	Diabetic ketoacid osis[c,e,g]	Lactic acidosis
Nervous system disorders		Taste disturbance[f] Dizziness			
Gastrointestinal disorders	Gastrointestinal symptoms[f]		Constipation[e] Dry mouth[e,f]		
Hepatobiliary disorders					Liver function disorders[f] Hepatitis[f]
Skin and subcutaneous tissue disorders					Urticaria[f] Erythema[f] Pruritus[f]
Musculoskeletal and connective tissue disorders		Back pain*	Nocturia**		
Renal and urinary disorders		Dysuria Polyuria[f]	Vulvovaginal pruritus** Pruritus genital**		
Reproductive system and breast disorders					
Investigations		Haematocrit increased[c] Creatinine renal clearance decreased during unitial treatment[c] Dyslipidaemia			

*The table shows adverse reactions identified from up to 24-week (short-term) data regardless of glycaemic rescue, except those marked with §.
*See corresponding subsection below for additional information.
[a]Vulvovaginitis, balanitis and related genital infections includes, e.g. the predefined preferred terms: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess.
[b]Urinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis.
[c]Volume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia, hypotension.
[d]Polyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.
[e]Mean changes from baseline in haematocrit were 2.30% for dapagliflozin 10 mg versus -0.33% for placebo. aematocrit values > 55% were reported in 1.3% of the subjects treated with dapagliflozin 10 mg versus 0.4% of placebo subjects.
[f]Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.
[g]Mean percent change from baseline for dapagliflozin 10 mg versus placebo, respectively, was: total cholesterol 2.5% versus 0.0%; HDL cholesterol 6.3% versus 2.7%; LDL cholesterol 2.9% versus -1.0%; triglycerides 2.7% versus -0.7%.
See section 4.2.
*Reported in the cardiovascular outcomes study in patients with type 2 diabetes (DECLARE). Frequency is based on annual rate.
**Adverse reactions were identified through post-marketing surveillance with the use of dapagliflozin. Rash includes the following preferred terms, listed in order of frequency in clinical trials: rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous. In active- and placebo-controlled clinical trials (dapagliflozin, N=6936; All control, N=9403), the frequency of rash was similar for dapagliflozin (1.4%) and all control (1.4%), respectively.
Reported in ≥ 2% of subjects and ≥ 1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.
Reported by the investigator as possibly related, probably related or related to study treatment and reported in ≥ 0.2% of subjects and ≥ 0.1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.
[a]Adverse reaction and frequency categories for metformin are based on information from the metformin Summary of Product Characteristics available in the European Union.

Overdose
Removal of dapagliflozin by haemodialysis has not been studied. The most effective method to remove metformin and lactate is haemodialysis.
Dapagliflozin
Dapagliflozin did not show any toxicity in healthy subjects at single-oral doses up to 500 mg (50 times the maximum recommended human dose). These subjects had detectable glucose in the urine for a dose-related period of time (at least 5 days for the 500 mg dose), with no reports of dehydration, hypotension or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycaemia was similar to placebo. In clinical studies where once daily doses of up to 100 mg (10 times the maximum recommended human dose) were administered for 2 weeks in healthy subjects and type 2 diabetes subjects, the incidence of hypoglycaemia was slightly higher than placebo and was not dose-related. Rates of adverse events including dehydration or hypotension were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters, including serum electrolytes and biomarkers of renal function.
In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

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

Dosage forms and packaging available
3 alu/alu blister packs in a cardboard box. Each alu/alu blister pack contains 10 tablets to make a box of 30 tablets.

Storage condition
Store at a temperature not exceeding 30°C. Protected from light and moisture.
Keep the medicine out of reach of children.

Prescription and delivery conditions
Liste-4 Only by prescription.

Marketing Authorization holder and Manufacturer :
UNISON PHARMACEUTICALS PVT LTD.
Unit-III, C-7,8,9, Steel Town, Opp. Nova Petro,
Moraiya, Ta - Sanand, Dist.: Ahmedabad-382213,Gujarat, India.

Date of last revision of the text: September 2024

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GSM of Paper 40 gsm **Colour of Paper** White **Colour of Matter** P P Black C **Pharmacode** 856 **Any other special process** N.A.

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