

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medical Product

1.1 Product Name : DIAZAC M ER

1.2 Strength :

DIAZAC M ER 5/1000

Each Film Coated Tablet Contains:

Dapagliflozin5 mg

Metformin Hydrochloride USP.....1000 mg

(As Extended Release)

Colour: Red Iron Oxide, Yellow Iron Oxide and Titanium dioxide

Excipientsq.s.

DIAZAC M ER 10/500

Each Film Coated Tablet Contains:

Dapagliflozin10 mg

Metformin Hydrochloride USP.....500 mg

(As Extended Release)

Colour: Red Iron Oxide, Yellow Iron Oxide and Titanium dioxide

Excipientsq.s.

DIAZAC M ER 10/1000

Each Film Coated Tablet Contains:

Dapagliflozin10 mg

Metformin Hydrochloride USP.....1000 mg

(As Extended Release)

Colour: Red Iron Oxide, Yellow Iron Oxide and Titanium dioxide

Excipientsq.s.

1.3 Pharmaceutical Dosage Form : Film Coated Tablet

2. Qualitative & Quantitative Composition:

DIAZAC M ER 5/1000

Each Film Coated Tablet Contains:

Dapagliflozin5 mg

Metformin Hydrochloride USP.....1000 mg

(As Extended Release)

Colour: Red Iron Oxide, Yellow Iron Oxide and Titanium dioxide

Excipientsq.s.

DIAZAC M ER 10/500

Each Film Coated Tablet Contains:

Dapagliflozin10 mg

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Colour: Red Iron Oxide, Yellow Iron Oxide and Titanium dioxide

Excipientsq.s.

DIAZAC M ER 10/1000

Each Film Coated Tablet Contains:

Dapagliflozin10 mg

Metformin Hydrochloride USP.....1000 mg

(As Extended Release)

Colour: Red Iron Oxide, Yellow Iron Oxide and Titanium dioxide

Excipientsq.s.

For a full list of excipients, see section 6.1 of SmPC

3. Pharmaceutical Form:

Film Coated Tablet

DIAZAC M ER 5/1000

Pink to dark pink coloured, oval shaped, biconvex, film-coated tablet, plain on both sides.

DIAZAC M ER 10/500

Pink coloured, oval shaped, biconvex, film-coated tablet, plain on both sides.

DIAZAC M ER 10/1000

Light yellow to yellow coloured, oval shaped, biconvex, film-coated tablet, plain on both sides.

4. Clinical Particulars

4.1 Therapeutic Indications:

DIAZAC M ER is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Dapagliflozin is indicated to reduce

- The risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors.
- The risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction.

Limitations of Use

- DIAZAC M ER is not recommended for patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.
- Because of the metformin component, the use of DIAZAC M ER is limited to adults with type 2 diabetes mellitus for all indications.

4.2 Posology and Method of administration:

Prior to initiation of Dapagliflozin / Metformin ER

- Assess renal function before initiating Dapagliflozin/Metformin ER therapy and periodically thereafter.
- Assess volume status and, if necessary, correct volume depletion prior to initiation of Dapagliflozin/Metformin ER

Recommended Administration

Take Dapagliflozin/Metformin ER once daily in the morning with food.

Swallow Dapagliflozin/Metformin ER tablets whole and never crush, cut, or chew.

Recommended Dosage

Individualize the starting dose of Dapagliflozin / Metformin ER based upon the patient's current regimen.

To improve glycemic control for patients not already taking dapagliflozin, the recommended starting dose for dapagliflozin is 5 mg once daily.

For indications related to heart failure, the recommended dose for dapagliflozin is 10 mg once daily.

Dosing may be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 10 mg dapagliflozin and 2000 mg metformin HCl.

Pediatric Use

Safety and effectiveness of Dapagliflozin/Metformin ER in pediatric patients under 18 years of age have not been established.

Geriatric Use

No Dapagliflozin/Metformin ER dosage change is recommended based on age. More frequent assessment of renal function is recommended in elderly patients

Patients with Renal Impairment

Dapagliflozin / Metformin ER is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m²

No dose adjustment for Dapagliflozin/Metformin ER is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m².

Dapagliflozin/Metformin ER is not recommended in patients with an eGFR below 45 mL/min/1.73m².

Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue Dapagliflozin / Metformin ER at the time of, or prior to, an iodinated contrast imaging procedure in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart Dapagliflozin / Metformin ER if renal function is stable

4.3 Contraindications:

Dapagliflozin / Metformin ER is contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m²), end stage renal disease or patients on dialysis.
- History of a serious hypersensitivity reaction to dapagliflozin or hypersensitivity to metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

4.4 Special warning and precautions for use:

Lactic Acidosis

There have been post-marketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate: pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of Dapagliflozin / Metformin ER.

In Dapagliflozin / Metformin ER-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin HCl is dialyzable, with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue Dapagliflozin/Metformin ER and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment

The post-marketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include:

- Before initiating Dapagliflozin / Metformin ER, obtain an estimated glomerular filtration rate (eGFR).
- Dapagliflozin / Metformin ER is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m².
- Obtain an eGFR at least annually in all patients taking Dapagliflozin / Metformin ER. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Drug Interactions

The concomitant use of Dapagliflozin / Metformin ER with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation (e.g., cationic drugs). Therefore, consider more frequent monitoring of patients.

Age 65 Or Greater

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.

Radiological Studies with Contrast

Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop Dapagliflozin / Metformin ER at the time of, or prior to, an iodinated contrast imaging procedure in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart Dapagliflozin / Metformin ER if renal function is stable.

Surgery and Other Procedures

Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. Dapagliflozin / Metformin ER should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States

Several of the post-marketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when

accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue Dapagliflozin/ Metformin ER.

Excessive Alcohol Intake

Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving Dapagliflozin/ Metformin ER.

Hepatic Impairment

Patients with hepatic impairment have developed with cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of Dapagliflozin / Metformin ER in patients with clinical or laboratory evidence of hepatic disease.

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 sodium-glucose co-transporter 2 (SGLT2) inhibitors, including dapagliflozin. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m²), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating Dapagliflozin/ Metformin ER 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.

Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in patients with type 1 and type 2 diabetes mellitus taking sodium-glucose co transporter 2 (SGLT2) inhibitors, including dapagliflozin. Fatal cases of ketoacidosis have been reported in patients taking dapagliflozin. Dapagliflozin/ Metformin ER is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with Dapagliflozin/ Metformin ER who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of blood glucose levels as ketoacidosis associated with Dapagliflozin/ Metformin ER may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, Dapagliflozin/ Metformin ER should be discontinued, the patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid, and carbohydrate replacement.

In many of the post-marketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized,

and the institution of treatment was delayed because the presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis, such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating Dapagliflozin/Metformin ER, 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/Metformin ER for at least 3 days prior to surgery.

Consider monitoring for ketoacidosis and temporarily discontinuing Dapagliflozin/ Metformin ER 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/Metformin ER.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue Dapagliflozin/Metformin ER and seek medical attention immediately if signs and symptoms occur.

Urosepsis and Pyelonephritis

There have been post-marketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization 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.

Hypoglycaemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues (e.g., sulfonylurea) are known to cause hypoglycemia. Dapagliflozin/Metformin ER may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with Dapagliflozin/Metformin ER.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier's 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 / Metformin ER 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/ Metformin ER, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Vitamin B12 Concentrations

In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. 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. Measure hematologic parameters on an annual basis and vitamin B12 at 2-to 3-year intervals in patients on Dapagliflozin / Metformin ER and manage any abnormalities.

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 and treat appropriately.

4.5 Interactions with other medicinal products and other forms of Interactions :

Positive Urine Glucose Test

Dapagliflozin

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.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Dapagliflozin

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 alternative methods to monitor glycemic control.

Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis.

Concomitant use of these drugs with Dapagliflozin/Metformin ER may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients.

Drugs That Reduce Metformin Clearance

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, such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use.

Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving Dapagliflozin / Metformin ER.

Drugs Affecting Glycemic Control

Metformin HCL

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These medications include thiazides and other diuretics, corticosteroids, phenothiazine, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving Dapagliflozin/Metformin ER, observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving Dapagliflozin/Metformin ER, observe the patient closely for hypoglycemia.

4.6 Pregnancy and Lactation:

Pregnancy

Based on animal data showing adverse renal effects, Dapagliflozin/Metformin ER is not recommended during the second and third trimesters of pregnancy.

Limited data with Dapagliflozin/Metformin ER or dapagliflozin in pregnant women are not sufficient to determine drug-associated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk (see Data). There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy (see Clinical Considerations). In animal studies, adverse renal pelvic and tubule dilatations, that were not fully reversible, were observed in rats when dapagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at all doses tested; the lowest of which provided an exposure 15-times the 10 mg clinical dose

Lactation

There is no information regarding the presence of Dapagliflozin/Metformin ER or dapagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production.

Limited published studies report that metformin is present in human milk (see Data). However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Dapagliflozin is present in the milk of lactating rats (see Data). However, due to species specific differences in lactation physiology, the clinical relevance of these data are not clear. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in breastfed infants, advise women that use of Dapagliflozin/Metformin ER is not recommended while breastfeeding.

4.7 Effects on ability to drive and use machine:

Not Applicable.

4.8 Undesirable Effects:

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Dapagliflozin and Metformin HCl

Data from a pre-specified pool of patients from 8 short-term, placebo-controlled studies of dapagliflozin co-administered with metformin immediate-or extended-release was used to evaluate safety. This pool included several add-on studies (metformin alone and in combination with a dipeptidyl peptidase-4 [DPP4] inhibitor and metformin, or insulin and metformin, 2 initial combinations with metformin studies, and 2 studies of patients with CVD and type 2 diabetes who received their usual treatment [with metformin as background therapy]). For studies that included background therapy with and without metformin, only patients who received metformin were included in the 8-study placebo-controlled pool. Across these 8 studies 983 patients were treated once daily with dapagliflozin 10 mg and metformin and 1185 were treated with placebo and metformin. These 8 studies provide a mean duration of exposure of 23 weeks. The mean age of the population was 57 years and 2% were older than 75 years. Fifty-four percent (54%) of the population was male; 88% White, 6% Asian, and 3% Black or African American. At baseline, the population had diabetes for an average of 8 years, mean hemoglobin A1c (HbA1c) was 8.4%, and renal function was normal or mildly impaired in 90% of patients and moderately impaired in 10% of patients.

The overall incidence of adverse events for the 8-study, short-term, placebo-controlled pool in patients treated with dapagliflozin 10 mg and metformin was 60.3% compared to 58.2% for the placebo and metformin group. Discontinuation of therapy due to adverse events in patients who received dapagliflozin 10 mg and metformin was 4% compared to 3.3% for the placebo and metformin group. The most commonly reported events leading to discontinuation and reported in at least 3 patients treated with dapagliflozin 10 mg and metformin were renal impairment (0.7%), increased blood creatinine (0.2%), decreased renal creatinine clearance (0.2%), and urinary tract infection (0.2%).

Table 1 shows common adverse reactions associated with the use of dapagliflozin and metformin. These adverse reactions were not present at baseline, occurred more commonly on dapagliflozin and metformin than on placebo, and occurred in at least 2% of patients treated with either dapagliflozin 5 mg or dapagliflozin 10 mg.

Table 1: Adverse Reactions in Placebo-Controlled Studies Reported in ≥2% of Patients Treated with Dapagliflozin and Metformin

Adverse Reaction	% of Patients		
	Pool of 8 Placebo-Controlled Studies		
	Placebo and Metformin N=1185	Dapagliflozin 5 mg and Metformin N=410	Dapagliflozin 10 mg and Metformin N=983
Female genital mycotic infections*	1.5	9.4	9.3
Nasopharyngitis	5.9	6.3	5.2
Urinary tract infections†	3.6	6.1	5.5
Diarrhea	5.6	5.9	4.2
Headache	2.8	5.4	3.3
Male genital mycotic infections‡	0	4.3	3.6
Influenza	2.4	4.1	2.6
Nausea	2.0	3.9	2.6
Back pain	3.2	3.4	2.5
Dizziness	2.2	3.2	1.8
Cough	1.9	3.2	1.4
Constipation	1.6	2.9	1.9
Dyslipidemia	1.4	2.7	1.5
Pharyngitis	1.1	2.7	1.5
Increased urination§	1.4	2.4	2.6
Discomfort with urination	1.1	2.2	1.6

* Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for females: vulvovaginal mycotic infection, vaginal infection, genital infection, vulvovaginitis, fungal genital infection, vulvovaginal candidiasis, vulval abscess, genital candidiasis, and vaginitis bacterial. (N for females: Placebo and metformin=534, dapagliflozin 5 mg and metformin=223, dapagliflozin 10 mg and metformin=430).

† Urinary tract infections include the following adverse reactions, listed in order of frequency reported: urinary tract infection, cystitis, pyelonephritis, urethritis, and prostatitis.

‡ Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection, posthitis, and balanoposthitis. (N for males: Placebo and metformin=651, dapagliflozin 5 mg and metformin=187, dapagliflozin 10 mg and metformin=553).

§ Increased urination includes the following adverse reactions, listed in order of frequency reported: pollakiuria, polyuria, and urine output increased.

Note for Tanzania: Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the TMDA ADR reporting tool; website: <https://imis.tmda.go.tz/arrt> or search for TMDA Adverse Reactions Reporting Tool in the Google Play Store.

Reporting of suspected adverse reactions

Health care professionals are asked to report any suspected adverse reactions via the <https://pv.pharmacyboardkenya.org>

4.9 Overdosage:

Metformin HCL

In placebo-controlled monotherapy trials of metformin extended-release, diarrhea and nausea/vomiting were reported in >5% of metformin-treated patients and more commonly than in placebo-treated patients (9.6% versus 2.6% for diarrhea and 6.5% versus 1.5% for nausea/vomiting). Diarrhea led to discontinuation of study medication in 0.6% of the patients treated with metformin extended-release.

Post-marketing Experience

Dapagliflozin

Additional adverse reactions have been identified during post-approval use of dapagliflozin. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Ketoacidosis
- Acute Kidney Injury
- Urosepsis and Pyelonephritis
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
- Rash

Metformin HCL

Cholestatic, hepatocellular, and mixed hepatocellular liver injury.

5. Pharmacological properties

5.1 Pharmacodynamic Properties:

Pharmacotherapeutic group: Antihyperglycemic

ATC Code:

Dapagliflozin : A10BK01

Metformin : A10BA02

Mechanism of Action

Dapagliflozin / Metformin ER

Dapagliflozin / Metformin ER combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and metformin HCl, a biguanide.

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.

Metformin HCl

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.

5.2 Pharmacokinetics Properties:

Dapagliflozin / Metformin ER

The administration of Dapagliflozin / Metformin ER in healthy subjects after a standard meal compared to the fasted state resulted in the same extent of exposure for both dapagliflozin and metformin extended-release. Compared to the fasted state, the standard meal resulted in 35% reduction and a delay of 1 to 2 hours in the peak plasma concentrations of dapagliflozin. This effect of food is not considered to be clinically meaningful. Food has no relevant effect on the pharmacokinetics of metformin when administered as Dapagliflozin / Metformin ER combination tablets.

Absorption

Dapagliflozin

Following oral administration of dapagliflozin, the maximum plasma concentration (C_{max}) is usually attained 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%. 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 and dapagliflozin can be administered with or without food.

Metformin HCl

Following a single oral dose of metformin extended-release, C_{max} is achieved with a median value of 7 hours and a range of 4 to 8 hours. The extent of metformin absorption (as measured by AUC) from the metformin extended-release tablet increased by approximately 50% when given with food. There was no effect of food on C_{max} and T_{max} of metformin.

Distribution

Dapagliflozin

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with renal or hepatic impairment.

Metformin HCl

Distribution studies with extended-release metformin have not been conducted; however, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes.

Metabolism

Dapagliflozin

The metabolism of dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% of a 50 mg [14C]-dapagliflozin dose and is the predominant drug-related component in human plasma.

Metformin HCl

Intravenous single-dose studies in healthy subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

Metabolism studies with extended-release metformin tablets have not been conducted.

Elimination

Dapagliflozin

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [14C]-dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life ($t_{1/2}$) for dapagliflozin is approximately 12.9 hours following a single oral dose of dapagliflozin 10 mg.

Metformin HCl

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

5.3 Preclinical Safety data:

Carcinogenesis, Mutagenesis, Impairment of Fertility

Dapagliflozin / Metformin ER

No animal studies have been conducted with Dapagliflozin / Metformin ER to evaluate carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on the findings in the studies with dapagliflozin and metformin individually.

Dapagliflozin

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.

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.

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 HCl

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 and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human dose of 2000 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.

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.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human dose based on body surface area comparisons.

6. Pharmaceutical particulars

6.1 List of Excipients:

DIAZAC M ER 5/1000

Microcrystalline Cellulose , Castor oil, Isopropyl Alcohol, Crospovidone, Colloidol Silicon dioxide, Magnesium Stearate, Hypromellose, Yellow iron oxide, Instacoat Orange, Opadry II brown.

DIAZAC M ER 10/500 & DIAZAC M ER 10/1000

Microcrystalline Cellulose , Castor oil, Isopropyl Alcohol, Crospovidone, Colloidol Silicon dioxide, Magnesium Stearate, Hypromellose, Red iron oxide, Instacoat Pink, Instacoat yellow.

6.2 Incompatibilities: Not applicable

6.3 Shelf life: 24 months

6.4 Special Precautions for storage: Do not store above 30°C.

Store below 30°C

6.5 Nature and contents of container:

10 tablets in Alu-Alu Blister pack, 3 such blisters in a printed carton along with pack Insert.

6.6 Special precautions for disposal: Not applicable

7. Marketing Authorization Holder:

Ajanta Pharma Limited
Ajanta House,
Charkop, Kandivli (West),
Mumbai- 400 067,
India

Manufacturing Site Address:

Ajanta Pharma Limited
Gut. No. 11/12/14/15, Chitegaon,
Paithan road. Aurangabad 431105
Maharashtra state, India

8. Marketing Authorization Numbers:

DIAZAC M ER 5/1000: H2025/CTD12088/25514
DIAZAC M ER 10/500: H2025/CTD12089/25539
DIAZAC M ER 10/1000: H2025/CTD12090/25584

9. Date of first registration /renewal of the registration:

08.07.2025

10. Date of revision of text:

08.07.2025