1.5 PRODUCT INFORMATION

1.5.1 Prescribing information (Summary of Product Characteristics)

1. NAME OF THE MEDICINAL PRODUCT:

Diajard-MXR 10/1000mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each film coated tablet contains:
Empagliflozin (as immediate release layer) …….. 10mg
Metformin HCl (as extended-release layer) …….. 1000mg.

3. PHARMACEUTICAL FORM:

Light Orange to orange Oblong Biconvex Film Coated Tablet.

4. CLINICAL PARTICULARS:

4.1. Therapeutic indications:

DIAJARD MXR is a combination of empagliflozin and metformin hydrochloride indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and metformin hydrochloride is appropriate.

4.2. Posology and method of administration:

Posology

In patients with volume depletion not previously treated with empagliflozin, correct this condition before initiating DIAJARD MXR)].

•Individualize the starting dose of DIAJARD MXR based on the patient's current regimen:

− In patients on metformin hydrochloride, switch to DIAJARD MXR containing a similar total daily dose of metformin hydrochloride and a total daily dose of empagliflozin 10 mg;

− In patients on empagliflozin, switch to DIAJARD MXR containing the same total daily dose of empagliflozin and a total daily dose of metformin hydrochloride extended-release 1000 mg;

− In patients already treated with empagliflozin and metformin hydrochloride, switch to DIAJARD MXR containing the same total daily doses of empagliflozin and a similar total daily dose of metformin hydrochloride.

Adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of metformin hydrochloride 2000 mg and empagliflozin 25 mg.

• The dose of metformin hydrochloride should be gradually escalated to reduce the gastrointestinal side effects due to metformin hydrochloride.

• Take DIAJARD MXR orally once daily with a meal in the morning

• Swallow DIAJARD MXR tablets whole. Do not split, crush, dissolve, or chew before swallowing. There have been reports of incompletely dissolved tablets being eliminated in the feces for other tablets containing metformin hydrochloride extended-release. If a patient reports seeing tablets in feces, the healthcare provider should assess adequacy of glycemic control.

• DIAJARD MXR 10 mg/1000 mg and 25 mg/1000 mg tablets should be taken as a single tablet once daily. DIAJARD MXR 5 mg/1000 mg and 12.5 mg/1000 mg tablets should be taken as two tablets together once daily.

2.2 Recommended Dosage in Patients with Renal Impairment
• Assess renal function prior to initiation of DIAJARD MXR and periodically, thereafter.

• DIAJARD MXR is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m.

Discontinuation for Iodinated Contrast Imaging Procedures
Discontinue DIAJARD MXR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m ; 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 DIAJARD MXR if renal function is stable.

4.3. Contraindication:

DIAJARD MXR is contraindicated in patients with:
• Moderate to severe renal impairment (eGFR less than 45 mL/min/1.73 m2), end stage renal disease, or dialysis.
• Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
• History of serious hypersensitivity reaction to empagliflozin or metformin.

4.4. Special warning and precautions for use:

Lactic Acidosis There have been postmarketing 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/Liter), 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 DIAJARD MXR. In DIAJARD MXR-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin is dialyzable, with a clearance of up to 170 mL/minute 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 DIAJARD MXR 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 postmarketing 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.

Before initiating DIAJARD MXR, obtain an estimated glomerular filtration rate (eGFR).

• DIAJARD MXR is contraindicated in patients with an eGFR below 45 mL/min/1.73 m2.

• Obtain an eGFR at least annually in all patients taking DIAJARD MXR. 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 DIAJARD MXR 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 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 DIAJARD MXR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m2 ; 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 DIAJARD MXR 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. DIAJARD MXR should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States: Several of the postmarketing 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 DIAJARD MXR.

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 DIAJARD MXR.

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

Hypotension:

Empagliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiating empagliflozin particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating DIAJARD MXR, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension after initiating therapy and increase monitoring in clinical situations where volume contraction is expected.

Ketoacidosis:

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus

receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including empagliflozin. Fatal cases of ketoacidosis have been reported in patients taking empagliflozin. DIAJARD MXR is not indicated for the treatment of patients with type 1 diabetes mellitus. Patients treated with DIAJARD MXR who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with DIAJARD MXR may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, DIAJARD MXR should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement. In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because 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 due to illness or surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified. Before initiating DIAJARD MXR, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. In patients treated with DIAJARD MXR consider monitoring for ketoacidosis and temporarily discontinuing DIAJARD MXR in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

Acute Kidney Injury and Impairment in Renal Function:

Empagliflozin causes intravascular volume contraction and can cause renal impairment. here have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors, including empagliflozin; some reports involved patients younger than 65 years of age. Before initiating DIAJARD MXR, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing DIAJARD MXR in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue DIAJARD MXR promptly and institute treatment. Empagliflozin increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating DIAJARD MXR. Renal function should be evaluated prior to initiation of DIAJARD MXR and monitored periodically thereafter. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m2. Use of DIAJARD MXR is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m2.

Urosepsis and Pyelonephritis:

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including empagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues:

Empagliflozin

Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when empagliflozin is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with DIAJARD MXR.

Metformin

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as SUs and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking β-adrenergic blocking drugs. Monitor for a need to lower the dose of DIAJARD MXR to minimize the risk of hypoglycemia in these patients.

Genital Mycotic Infections:

Empagliflozin increases the risk for genital mycotic infections. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop mycotic genital infections. Monitor and treat as appropriate.

Vitamin B12 Levels:

In controlled, 29-week clinical trials of metformin, a decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anemia or neurologic manifestations due to the short duration.

Increased Low-Density Lipoprotein Cholesterol (LDL-C):

Increases in LDL-C can occur with empagliflozin. Monitor and treat as appropriate.

4.5. Interaction with other medicinal products and other forms of interactions:

Drug Interactions with Empagliflozin

Diuretics: Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.

Insulin or Insulin Secretagogues: Coadministration of empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia.

Positive Urine Glucose Test: Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay: Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

Drug Interactions with Metformin Hydrochloride:

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.

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 DIAJARD MXR may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients

Drugs Affecting Glycemic Control: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving DIAJARD MXR, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving DIAJARD MXR, the patient should be observed closely for hypoglycemia.

Alcohol: Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving DIAJARD MXR.

4.6. Fertility, Pregnancy, and lactation:

Pregnancy:

Pregnancy Risk Summary Based on animal data showing adverse renal effects, DIAJARD MXR is not recommended during the second and third trimesters of pregnancy. Limited available data with DIAJARD MXR or empagliflozin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy. In animal studies, adverse renal changes were observed in rats when empagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 13-times the maximum clinical dose caused renal pelvic and tubule dilatations that were reversible. Empagliflozin was not teratogenic in rats and rabbits up to 300 mg/kg/day, which approximates 48 times and 128-times, respectively, the maximum clinical dose of 25 mg when administered during organogenesis. No adverse developmental effects were observed when metformin was administered to pregnant Sprague Dawley rats and rabbits during the period of organogenesis at doses up to 2- and 6-times, respectively, a 2000 mg clinical dose, based on body surface area (see Data). The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Clinical Considerations Disease-associated maternal and/or embryo/fetal risk: Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity. Data Human Data Published data from post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups. Animal Data Empagliflozin: Empagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 10, 30 and 100 mg/kg/day caused increased kidney weights and renal tubular and pelvic dilatation at 100 mg/kg/day, which approximates 13-times the maximum clinical dose of 25 mg, based on AUC. These findings were not observed after a 13-week drug-free recovery period. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development. In embryo-fetal development studies in rats and rabbits, empagliflozin was administered for intervals coinciding with the first trimester period of

organogenesis in humans. Doses up to 300 mg/kg/day, which approximates 48 times (rats) and 128-times (rabbits) the maximum clinical dose of 25 mg (based on AUC), did not result in adverse developmental effects. In rats, at higher doses of empagliflozin causing maternal toxicity, malformations of limb bones increased in fetuses at 700 mg/kg/day or 154-times the 25 mg maximum clinical dose. In the rabbit, higher doses of empagliflozin resulted in maternal and fetal toxicity at 700 mg/kg/day, or 139-times the 25 mg maximum clinical dose. In pre- and postnatal development studies in pregnant rats, empagliflozin was administered from gestation day 6 through to lactation day 20 (weaning) at up to 100 mg/kg/day (approximately 16-times the 25 mg maximum clinical dose) without maternal toxicity. Reduced body weight was observed in the offspring at greater than or equal to 30 mg/kg/day (approximately 4-times the 25 mg maximum clinical dose). Metformin hydrochloride: Metformin hydrochloride did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits at up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of approximately 2- and 6-times a clinical dose of 2000 mg, based on body surface area (mg/m2) for rats and rabbits, respectively. Empagliflozin and Metformin hydrochloride: No adverse developmental effects were observed when empagliflozin and metformin hydrochloride were coadministered to pregnant rats during the period of organogenesis at exposures of approximately 35- and 14-times the clinical AUC exposure of empagliflozin associated with the 10 mg and 25 mg doses, respectively, and 4-times the clinical AUC exposure of metformin associated with the 2000 mg dose.

Lactation:

Risk Summary There is no information regarding the presence of DIAJARD MXR or empagliflozin 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. 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. Empagliflozin is present in the milk of lactating rats. 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 a breastfed infant, advise women that use of DIAJARD MXR is not recommended while breastfeeding. Data Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants. Empagliflozin was present at a low level in rat fetal tissues after a single oral dose to the dams at gestation day 18. In rat milk, the mean milk to plasma ratio ranged from 0.634 -5, and was greater than one from 2 to 24 hours post-dose. The mean maximal milk to plasma ratio of 5 occurred at 8 hours post-dose, suggesting accumulation of empagliflozin in the milk. Juvenile rats directly exposed to empagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

Females and Males of Reproductive Potential:

Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

4.7. Effects on ability to drive and use machines:

Diajard MXR has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects:

The following important adverse reactions are described below and elsewhere in the labeling:

- Lactic Acidosis
- Hypotension
- Ketoacidosis
- Acute Kidney Injury and Impairment in Renal Function
- Urosepsis and Pyelonephritis
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
- Genital Mycotic Infections
- Vitamin B12 Deficiency
- Increased Low-Density Lipoprotein Cholesterol (LDL-C).

4.9. Overdoses:

In the event of an overdose with DIAJARD MXR, contact the Poison Control Center. Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of empagliflozin by hemodialysis has not been studied. However, metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful partly for removal of accumulated metformin from patients in whom DIAJARD MXR overdosage is suspected. Metformin hydrochloride Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Diajard-MXR 10/1000mg Tablet
(Empagliflozin + Metformin HCl)
(Film Coated Tablet)

Summary of Product characteristics
Ministry of Health
Kenya

HIGHNOON LABORATORIES LIMITED

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs

ATC code: A10BD20

Mechanism of action

Diajard MXR combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: empagliflozin, an inhibitor of sodium-glucose co-transporter 2 (SGLT2), and metformin hydrochloride, a member of the biguanide class.

Empagliflozin

Empagliflozin is a reversible, highly potent (IC50 of 1.3 nmol) and selective competitive inhibitor of SGLT2. Empagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 5000-times more selective for SGLT2 versus SGLT1, the major transporter responsible for glucose absorption in the gut. SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible, as the predominant transporter, for the reabsorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes and hyperglycaemia a higher amount of glucose is filtered and reabsorbed.

Empagliflozin improves glycaemic control in patients with type 2 diabetes by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent on blood glucose concentration and GFR. Inhibition of SGLT2 in patients with type 2 diabetes and hyperglycaemia leads to excess glucose excretion in the urine. In addition, initiation of empagliflozin increases excretion of sodium resulting in osmotic diuresis and reduced intravascular volume.

In patients with type 2 diabetes, urinary glucose excretion increased immediately following the first dose of empagliflozin and is continuous over the 24 hour dosing interval. Increased urinary glucose excretion was maintained at the end of the 4-week treatment period, averaging approximately 78 g/day with empagliflozin 25 mg. Increased urinary glucose excretion resulted in an immediate reduction in plasma glucose levels in patients with type 2 diabetes.

Empagliflozin improves both fasting and post-prandial plasma glucose levels. The mechanism of action of empagliflozin is independent of beta cell function and insulin pathway and this contributes to a low risk of hypoglycaemia. Improvement of surrogate markers of beta cell function including Homeostasis Model Assessment-β (HOMA-β) was noted. In addition, urinary glucose excretion triggers calorie loss, associated with body fat loss and body weight reduction. The glucosuria observed with empagliflozin is accompanied by mild diuresis which may contribute to sustained and moderate reduction of blood pressure. The glucosuria, natriuresis and osmotic

diuresis observed with empagliflozin may contribute to the improvement in cardiovascular outcomes.

Metformin

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

Metformin may act via 3 mechanisms:

• reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis,

• in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization,

• and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

Clinical efficacy and safety

Both improvement of glycaemic control and reduction of cardiovascular morbidity and mortality are an integral part of the treatment of type 2 diabetes.

Glycaemic efficacy and cardiovascular outcomes have been assessed in a total of 10,366 patients with type 2 diabetes who were treated in 9 double-blind, placebo or active-controlled clinical studies of at least 24 weeks duration, of which 2950 patients received empagliflozin 10 mg and 3701 received empagliflozin 25 mg as add-on to metformin therapy. Of these, 266 or 264 patients were treated with empagliflozin 10 mg or 25 mg as add-on to metformin plus insulin, respectively.

Treatment with empagliflozin in combination with metformin with or without other antidiabetic medicinal products (pioglitazone, sulfonylurea, DPP-4 inhibitors, and insulin) led to clinically relevant improvements in HbA1c, fasting plasma glucose (FPG), body weight, systolic and diastolic blood pressure. Administration of empagliflozin 25 mg resulted in a higher proportion of patients achieving HbA1c goal of less than 7% and fewer patients needing glycaemic rescue compared to empagliflozin 10 mg and placebo. In patients age 75 years and older, numerically lower reductions in HbA1c were observed with empagliflozin treatment. Higher baseline HbA1c was associated with a greater reduction in HbA1c. In addition, empagliflozin as adjunct to standard care therapy reduced cardiovascular mortality in patients with type 2 diabetes and established cardiovascular disease.

Empagliflozin as add-on to metformin, sulphonylurea, pioglitazone

Empagliflozin as add-on to metformin, metformin and a sulphonylurea, or pioglitazone and metformin resulted in statistically significant ($p<0.0001$) reductions in HbA1c and body weight compared to placebo (Table 3). In addition it resulted in a clinically meaningful reduction in FPG, systolic and diastolic blood pressure compared to placebo.

In the double-blind placebo-controlled extension of these studies, reduction of HbA1c, body weight and blood pressure were sustained up to Week 76.

Table 3: Efficacy results of 24 week placebo-controlled studies

Add-on to metformin therapya			
	Placebo	Empagliflozin	
		10 mg	25 mg
N	207	217	213
HbA1c (%)			
Baseline (mean)	7.90	7.94	7.86
Change from baseline1	-0.13	-0.70	-0.77
Difference from placebo1 (97.5% CI)		-0.57* (-0.72, -0.42)	-0.64* (-0.79, -0.48)
N	184	199	191
Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%2	12.5	37.7	38.7
N	207	217	213
Body Weight (kg)			
Baseline (mean)	79.73	81.59	82.21
Change from baseline1	-0.45	-2.08	-2.46
Difference from placebo1 (97.5% CI)		-1.63* (-2.17, -1.08)	-2.01* (-2.56, -1.46)
N	207	217	213
SBP (mmHg)2			
Baseline (mean)	128.6	129.6	130.0
Change from baseline1	-0.4	-4.5	-5.2
Difference from placebo1 (95% CI)		-4.1* (-6.2, -2.1)	-4.8* (-6.9, -2.7)

Add-on to metformin and a sulphonylurea therapya			
	Placebo	Empagliflozin	
		10 mg	25 mg
N	225	225	216
HbA1c (%)			
Baseline (mean)	8.15	8.07	8.10
Change from baseline1	-0.17	-0.82	-0.77
Difference from placebo1 (97.5% CI)		-0.64* (-0.79, -0.49)	-0.59* (-0.74, -0.44)
N	216	209	202
Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%2	9.3	26.3	32.2
N	225	225	216
Body Weight (kg)			
Baseline (mean)	76.23	77.08	77.50
Change from baseline1	-0.39	-2.16	-2.39
Difference from placebo1 (97.5% CI)		-1.76* (-2.25, -1.28)	-1.99* (-2.48, -1.50)
N	225	225	216
SBP (mmHg)2			
Baseline (mean)	128.8	128.7	129.3
Change from baseline1	-1.4	-4.1	-3.5
Difference from placebo1 (95% CI)		-2.7 (-4.6, -0.8)	-2.1 (-4.0, -0.2)
Add-on to pioglitazone + metformin therapyb			
	Placebo	Empagliflozin	
		10 mg	25 mg
N	124	125	127
HbA1c (%)			
Baseline (mean)	8.15	8.07	8.10
Change from baseline1	-0.11	-0.55	-0.70

Difference from placebo1 (97.5% CI)		-0.45* (-0.69, -0.21)	-0.60* (-0.83, -0.36)
N	118	116	123
Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%2	8.5	22.4	28.5
N	124	125	127
Body Weight (kg)			
Baseline (mean)	79.45	79.44	80.98
Change from baseline1	0.40	-1.74	-1.59
Difference from placebo1 (97.5% CI)		-2.14* (-2.93, -1.35)	-2.00* (-2.78, -1.21)
N	124	125	127
SBP (mmHg)2, 3			
Baseline (mean)	125.5	126.3	126.3
Change from baseline1	0.8	-3.5	-3.3
Difference from placebo1 (95% CI)		-4.2** (-6.94, -1.53)	-4.1** (-6.76, -1.37)

a Full analysis set (FAS) using last observation carried forward (LOCF) prior to glycaemic rescue therapy

b Subgroup analysis for patients on additional background of metformin (FAS, LOCF)

1 Mean adjusted for baseline value

2 Not evaluated for statistical significance as a part of the sequential confirmatory testing procedure

3 LOCF, values after antihypertensive rescue censored

* p-value <0.0001

** p-value <0.01

Empagliflozin in combination with metformin in drug-naïve patients

A factorial design study of 24 weeks duration was conducted to evaluate the efficacy and safety of empagliflozin in drug-naïve patients. Treatment with empagliflozin in combination with metformin (5 mg and 500 mg; 5 mg and 1000 mg; 12.5 mg and 500 mg, and 12.5 mg and 1000 mg given twice daily) provided statistically significant improvements in HbA1c (Table 4) and led

to greater reductions in FPG (compared to the individual components) and body weight (compared to metformin).

Table 4: Efficacy results at 24 week comparing empagliflozin in combination with metformin to the individual componentsa

	Empagliflozin 10 mg			Empagliflozin 25 mg			Metformin	
	+ Met 1000 mgc	+ Met 2000 mgc	No Met	+ Met 1000 mgc	+ Met 2000 mgc	No Met	1000 mg	2000 mg
N	161	167	169	165	169	163	167	162
HbA1c (%)								
Baseline (mean)	8.68	8.65	8.62	8.84	8.66	8.86	8.69	8.55
Change from baseline1	-1.98	-2.07	-1.35	-1.93	-2.08	-1.36	-1.18	-1.75
Comparison vs. empa (95% CI)1	-0.63* (-0.86, -0.40)	-0.72* (-0.96, -0.49)		-0.57* (-0.81, -0.34)	-0.72* (-0.95, -0.48)			
Comparison vs. met (95% CI)1	-0.79* (-1.03, -0.56)	-0.33* (-0.56, -0.09)		-0.75* (-0.98 -0.51)	-0.33* (-0.56, -0.10)			

Met = metformin; empa = empagliflozin

1 mean adjusted for baseline value

a Analyses were performed on the full analysis set (FAS) using an observed cases (OC) approach

b Given in two equally divided doses per day when given together with metformin

c Given in two equally divided doses per day

*p≤0.0062 for HbA1c

Empagliflozin in patients inadequately controlled with metformin and linagliptin

In patients inadequately controlled with metformin and linagliptin 5 mg, treatment with both empagliflozin 10 mg or 25 mg resulted in statistically significant (p<0.0001) reductions in HbA1c and body weight compared to placebo (Table 5). In addition it resulted in clinically meaningful reductions in FPG, systolic and diastolic blood pressure compared to placebo.

Table 5: Efficacy results of a 24 week placebo-controlled study in patients inadequately controlled with metformin and linagliptin 5 mg

Add-on to metformin and linagliptin 5 mg			
	Placebo5	Empagliflozin6	
		10 mg	25 mg
N	106	109	110
HbA1c (%)3			
Baseline (mean)	7.96	7.97	7.97
Change from baseline1	0.14	-0.65	-0.56
Difference from placebo (95% CI)		-0.79* (-1.02, -0.55)	-0.70* (-0.93, -0.46)
N	100	100	107
Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%2	17.0	37.0	32.7
N	106	109	110
Body Weight (kg)3			
Baseline (mean)	82.3	88.4	84.4
Change from baseline1	-0.3	-3.1	-2.5
Difference from placebo (95% CI)		-2.8* (-3.5, -2.1)	-2.2* (-2.9, -1.5)
N	106	109	110
SBP (mmHg)4			
Baseline (mean)	130.1	130.4	131.0
Change from baseline1	-1.7	-3.0	-4.3
Difference from placebo (95% CI)		-1.3 (-4.2, 1.7)	-2.6 (-5.5, 0.4)

1 Mean adjusted for baseline value

2 Not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints

3 MMRM model on FAS (OC) included baseline HbA1c, baseline eGFR (MDRD), geographical region, visit, treatment, and treatment by visit interaction. For weight, baseline weight was included.

4 MMRM model included baseline SBP and baseline HbA1c as linear covariate(s), and baseline eGFR, geographical region, treatment, visit, and visit by treatment interaction as fixed effects.

5 Patients randomized to the placebo group were receiving the placebo plus linagliptin 5 mg with background metformin

6 Patients randomized to the empagliflozin 10 mg or 25 mg groups were receiving empagliflozin 10 mg or 25 mg and linagliptin 5 mg with background metformin

* p-value <0.0001

In a prespecified subgroup of patients with baseline HbA1c greater or equal than 8.5% the reduction from baseline in HbA1c was -1.3% with empagliflozin 10 mg or 25 mg at 24 weeks (p<0.0001) compared to placebo.

Empagliflozin 24 months data, as add-on to metformin in comparison to glimepiride

In a study comparing the efficacy and safety of empagliflozin 25 mg versus glimepiride (up to 4 mg per day) in patients with inadequate glycaemic control on metformin alone, treatment with empagliflozin daily resulted in superior reduction in HbA1c (Table 6), and a clinically meaningful reduction in FPG, compared to glimepiride. Empagliflozin daily resulted in a statistically significant reduction in body weight, systolic and diastolic blood pressure and a statistically significantly lower proportion of patients with hypoglycaemic events compared to glimepiride (2.5% for empagliflozin, 24.2% for glimepiride, p<0.0001).

Table 6: Efficacy results at 104 week in an active controlled study comparing empagliflozin to glimepiride as add on to metformina

	Empagliflozin 25 mg	Glimepirideb
N	765	780
HbA1c (%)		
Baseline (mean)	7.92	7.92
Change from baseline1	-0.66	-0.55
Difference from glimepiride1 (97.5% CI)	-0.11* (-0.20, -0.01)	
N	690	715
Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%2	33.6	30.9
N	765	780
Body Weight (kg)		
Baseline (mean)	82.52	83.03
Change from baseline1	-3.12	1.34
Difference from glimepiride1 (97.5% CI)	-4.46** (-4.87, -4.05)	
N	765	780

SBP (mmHg)3		
Baseline (mean)	133.4	133.5
Change from baseline1	-3.1	2.5
Difference from glimepiride1 (97.5% CI)	-5.6** (-7.0,-4.2)	

a Full analysis set (FAS) using last observation carried forward (LOCF) prior to glycaemic rescue therapy

b Up to 4 mg glimepiride

1 Mean adjusted for baseline value

2 Not evaluated for statistical significance as a part of the sequential confirmatory testing procedure

3 LOCF, values after antihypertensive rescue censored

* p-value <0.0001 for non-inferiority, and p-value = 0.0153 for superiority

** p-value <0.0001

Add-on to insulin therapy

Empagliflozin as add-on to multiple daily insulin

The efficacy and safety of empagliflozin as add-on to multiple daily insulin with concomitant metformin therapy was evaluated in a double-blind, placebo-controlled trial of 52 weeks duration. During the initial 18 weeks and the last 12 weeks, the insulin dose was kept stable, but was adjusted to achieve pre-prandial glucose levels <100 mg/dl [5.5 mmol/l], and post-prandial glucose levels <140 mg/dl [7.8 mmol/l] between Weeks 19 and 40.

At Week 18, empagliflozin provided statistically significant improvement in HbA1c compared with placebo (Table 7).

At Week 52, treatment with empagliflozin resulted in a statistically significant decrease in HbA1c and insulin sparing compared with placebo and a reduction in body weight.

Table 7: Efficacy results at 18 and 52 weeks in a placebo-controlled study of empagliflozin as add-on to multiple daily doses of insulin with concomitant metformin therapy

	Placebo	empagliflozin	
		10 mg	25 mg
N	135	128	137
HbA1c (%) at week 18a			
Baseline (mean)	8.29	8.42	8.29

Change from baseline1	-0.58	-0.99	-1.03
Difference from placebo1 (97.5% CI)		-0.41* (-0.61, -0.21)	-0.45* (-0.65, -0.25)
N	86	84	87
HbA1c (%) at week 52b			
Baseline (mean)	8.26	8.43	8.38
Change from baseline1	-0.86	-1.23	-1.31
Difference from placebo1 (97.5% CI)		-0.37** (-0.67, -0.08)	-0.45* (-0.74, -0.16)
N	84	84	87
Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7% at week 52b, 2	27.4	41.7	48.3
N	86	83	86
Insulin dose (IU/day) at week 52b, 3			
Baseline (mean)	91.01	91.77	90.22
Change from baseline1	12.84	0.22	-2.25
Difference from placebo1 (97.5% CI)		-12.61** (-21.43, -3.80)	-15.09** (-23.79, -6.40)
N	86	84	87
Body Weight (kg) at week 52b			
Baseline (mean)	97.78	98.86	94.93
Change from baseline1	0.42	-2.47	-1.94
Difference from placebo1 (97.5% CI)		-2.89* (-4.29, -1.49)	-2.37* (-3.75, -0.98)

a Subgroup analysis for patients on additional background of metformin (FAS, LOCF)

b Subgroup analysis for patients on additional background of metformin (PPS-Completers, LOCF)

1 Mean adjusted for baseline value

2 not evaluated for statistical significance as a part of the sequential confirmatory testing procedure

3 Week 19-40: treat-to-target regimen for insulin dose adjustment to achieve pre-defined glucose target levels (pre-prandial <100 mg/dl (5.5 mmol/l), post-prandial <140 mg/dl (7.8 mmol/l)

* p-value ≤0.0005

** p-value <0.005

Empagliflozin as add on to basal insulin

The efficacy and safety of empagliflozin as add on to basal insulin with concomitant metformin therapy was evaluated in a double-blind, placebo-controlled trial of 78 weeks duration. During the initial 18 weeks the insulin dose was kept stable, but was adjusted to achieve a FPG <110 mg/dl in the following 60 weeks.

At week 18, empagliflozin provided statistically significant improvement in HbA1c. A greater proportion of patients treated with empagliflozin and with a baseline HbA1c ≥7.0% achieved a target HbA1c of <7% compared to placebo (Table 8).

At 78 weeks, the decrease in HbA1c and insulin sparing effect of empagliflozin was maintained. Furthermore, empagliflozin resulted in a reduction in FPG, body weight and blood pressure.

Table 8: Efficacy results at 18 and 78 weeks in a placebo-controlled study of empagliflozin as add on to basal insulin with metformina

	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg
N	96	107	99
HbA1c (%) at week 18			
Baseline (mean)	8.02	8.21	8.35
Change from baseline1	-0.09	-0.62	-0.72
Difference from placebo1 (97.5% CI)		-0.54* (-0.77, -0.30)	-0.63* (-0.88, -0.39)
N	89	105	94
HbA1c (%) at week 78			
Baseline (mean)	8.03	8.24	8.29
Change from baseline1	-0.08	-0.42	-0.71
Difference from placebo1 (97.5% CI)		-0.34** (-0.64, -0.05)	-0.63* (-0.93, -0.33)
N	89	105	94
Basal insulin dose (IU/day) at week 78			
Baseline (mean)	49.61	47.25	49.37
Change from baseline1	4.14	-2.07	-0.28

Difference from placebo1 (97.5% CI)		-6.21** (-11.81, -0.61)	-4.42 (-10.18, 1.34)

a Subgroup analysis of full analysis set (FAS) for patients on additional background of metformin - Completers using last observation carried forward (LOCF) prior to glycaemic rescue therapy

1 mean adjusted for baseline value

* p-value <0.0001

** p-value ≤0.025

Empagliflozin and linagliptin as add-on therapy to metformin

In a double-blind trial in patients with inadequate glycemic control, 24-weeks treatment with both doses of empagliflozin plus linagliptin as add-on to metformin therapy provided statistically significant (p<0.0001) reductions in HbA1c (change from baseline of -1.08% for empagliflozin 10 mg plus linagliptin 5 mg, -1.19% for empagliflozin 25 mg plus linagliptin 5 mg, -0.70% for linagliptin 5 mg). Compared to linagliptin 5 mg, both doses of empagliflozin plus linagliptin 5 mg provided statistically significant reductions in FPG and blood pressure. Both doses provided similar statistically significant reductions in body weight, expressed as kg and percentage change. A greater proportion of patients with a baseline HbA1c ≥7.0% and treated with empagliflozin plus linagliptin achieved a target HbA1c of <7% compared to linagliptin 5 mg. Clinically meaningful reductions in HbA1c were maintained for 52 weeks.

Empagliflozin twice daily versus once daily as add on to metformin therapy

The efficacy and safety of empagliflozin twice daily versus once daily (daily dose of 10 mg and 25 mg) as add-on therapy in patients with in sufficient glycemic control on metformin monotherapy was evaluated in a double blind placebo-controlled study of 16 weeks duration. All treatments with empagliflozin resulted in significant reductions in HbA1c from baseline (total mean 7.8%) after 16 weeks of treatment compared with placebo. Empagliflozin twice daily dose regimens on a background of metformin led to comparable reductions in HbA1c versus once daily dose regimens with a treatment difference in HbA1c reductions from baseline to week 16 of -0.02% (95% CI -0.16, 0.13) for empagliflozin 5 mg twice daily versus 10 mg once daily, and -0.11% (95% CI -0.26, 0.03) for empagliflozin 12.5 mg twice daily versus 25 mg once daily.

Cardiovascular outcome

The double-blind, placebo-controlled EMPA-REG OUTCOME study compared pooled doses of empagliflozin 10 mg and 25 mg with placebo as adjunct to standard care therapy in patients with type 2 diabetes and established cardiovascular disease. A total of 7020 patients were treated (empagliflozin 10 mg: 2345, empagliflozin 25 mg: 2342, placebo: 2333) and followed for a median of 3.1 years. The mean age was 63 years, the mean HbA1c was 8.1%, and 71.5% were male. At baseline, 74% of patients were being treated with metformin, 48% with insulin, and 43% with a

sulfonylurea. About half of the patients (52.2%) had an eGFR of 60-90 ml/min/1.73 m2, 17.8% of 45-60 ml/min/1.73 m2 and 7.7% of 30-45 ml/min/1.73 m2.

At week 12, an adjusted mean (SE) improvement in HbA1c when compared to baseline of 0.11% (0.02) in the placebo group, 0.65% (0.02) and 0.71% (0.02) in the empagliflozin 10 and 25 mg groups was observed. After the first 12 weeks glycaemic control was optimized independent of investigative treatment. Therefore the effect was attenuated at week 94, with an adjusted mean (SE) improvement in HbA1c of 0.08% (0.02) in the placebo group, 0.50% (0.02) and 0.55% (0.02) in the empagliflozin 10 and 25 mg groups.

Empagliflozin was superior in preventing the primary combined endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke, as compared with placebo. The treatment effect was driven by a significant reduction in cardiovascular death with no significant change in non-fatal myocardial infarction, or non-fatal stroke. The reduction of cardiovascular death was comparable for empagliflozin 10 mg and 25 mg (see Figure 1) and confirmed by an improved overall survival (Table 9).

The efficacy for preventing cardiovascular mortality has not been conclusively established in patients using empagliflozin concomitantly with DPP-4 inhibitors or in Black patients because the representation of these groups in the EMPA-REG OUTCOME study was limited.

Table 9: Treatment effect for the primary composite endpoint, its components and mortalitya

	Placebo	Empagliflozinb
N	2333	4687
Time to first event of CV death, non-fatal MI, or non-fatal stroke N (%)	282 (12.1)	490 (10.5)
Hazard ratio vs. placebo (95.02% CI)*		0.86 (0.74, 0.99)
p−value for superiority		0.0382
CV Death N (%)	137 (5.9)	172 (3.7)
Hazard ratio vs. placebo (95% CI)		0.62 (0.49, 0.77)
p-value		<0.0001
Non-fatal MI N (%)	121 (5.2)	213 (4.5)
Hazard ratio vs. placebo (95% CI)		0.87 (0.70, 1.09)
p−value		0.2189
Non-fatal stroke N (%)	60 (2.6)	150 (3.2)
Hazard ratio vs. placebo (95% CI)		1.24 (0.92, 1.67)
p−value		0.1638

All-cause mortality N (%)	194 (8.3)	269 (5.7)
Hazard ratio vs. placebo (95% CI)		0.68 (0.57, 0.82)
p-value		<0.0001
Non-CV mortality N (%)	57 (2.4)	97 (2.1)
Hazard ratio vs. placebo (95% CI)		0.84 (0.60, 1.16)

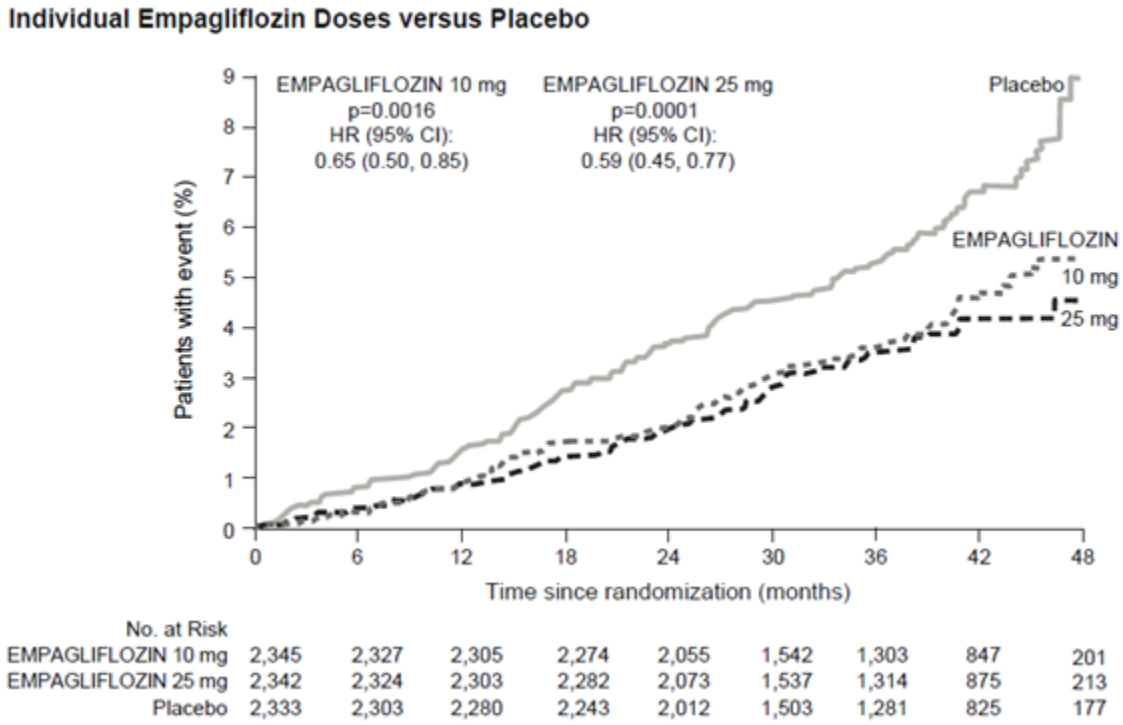
CV = cardiovascular, MI = myocardial infarction

a Treated set (TS), i.e. patients who had received at least one dose of study drug

b Pooled doses of empagliflozin 10 mg and 25 mg

* Since data from the trial were included in an interim analysis, a two-sided 95.02% confidence interval applied which corresponds to a p-value of less than 0.0498 for significance.

Figure 1 Time to occurrence of cardiovascular death in the EMPA-REG OUTCOME study



Heart failure requiring hospitalization

In the EMPA-REG OUTCOME study, empagliflozin reduced the risk of heart failure requiring hospitalization compared with placebo (empagliflozin 2.7 %; placebo 4.1 %; HR 0.65, 95 % CI 0.50, 0.85).

Nephropathy

In the EMPA-REG OUTCOME study, for time to first nephropathy event, the HR was 0.61 (95 % CI 0.53, 0.70) for empagliflozin (12.7 %) vs placebo (18.8 %).

In addition, empagliflozin showed a higher (HR 1.82, 95 % CI 1.40, 2.37) occurrence of sustained normo- or micro-albuminuria (49.7 %) in patients with baseline macro-albuminuria compared with placebo (28.8 %).

2 hour post-prandial glucose

Treatment with empagliflozin as add-on to metformin or metformin plus sulfonylurea resulted in clinically meaningful improvement of 2-hour post-prandial glucose (meal tolerance test) at 24 weeks (add-on to metformin, placebo: +5.9 mg/dl, empagliflozin 10 mg: -46.0 mg/dl, empagliflozin 25 mg: -44.6 mg/dl; add-on to metformin plus sulphonylurea, placebo: -2.3 mg/dl, empagliflozin 10 mg: -35.7 mg/dl, empagliflozin 25 mg: -36.6 mg/dl).

Patients with baseline HbA1c ≥9%

In a pre-specified analysis of subjects with baseline HbA1c ≥9.0%, treatment with empagliflozin 10 mg or 25 mg as add-on to metformin resulted in statistically significant reductions in HbA1c at Week 24 (adjusted mean change from baseline of -1.49% for empagliflozin 25 mg, -1.40% for empagliflozin 10 mg, and -0.44% for placebo).

Body weight

In a pre-specified pooled analysis of 4 placebo controlled studies, treatment with empagliflozin (68% of all patients were on metformin background) resulted in body weight reduction compared to placebo at week 24 (-2.04 kg for empagliflozin 10 mg, -2.26 kg for empagliflozin 25 mg and -0.24 kg for placebo) that was maintained up to week 52 (-1.96 kg for empagliflozin 10 mg, -2.25 kg for empagliflozin 25 mg and -0.16 kg for placebo).

Blood pressure

The efficacy and safety of empagliflozin was evaluated in a double-blind, placebo controlled study of 12 weeks duration in patients with type 2 diabetes and high blood pressure on different antidiabetic and up to 2 antihypertensive therapies. Treatment with empagliflozin once daily resulted in statistically significant improvement in HbA1c, and 24 hour mean systolic and diastolic blood pressure as determined by ambulatory blood pressure monitoring (Table 10). Treatment with empagliflozin provided reductions in seated SBP and DBP.

Table 10: Efficacy results at 12 week in a placebo-controlled study of empagliflozin in patients with type 2 diabetes and uncontrolled blood pressurea

	Placebo	empagliflozin	
		10 mg	25 mg
N	271	276	276
HbA1c (%) at week 121			
Baseline (mean)	7.90	7.87	7.92
Change from baseline2	0.03	-0.59	-0.62
Difference from placebo1 (95% CI)2		-0.62* (-0.72, -0.52)	-0.65* (-0.75, -0.55)
24 hour SBP at week 123			
Baseline (mean)	131.72	131.34	131.18
Change from baseline4	0.48	-2.95	-3.68
Difference from placebo4 (95% CI)		-3.44* (-4.78, -2.09)	-4.16* (-5.50, -2.83)
24 hour DBP at week 123			
Baseline (mean)	75.16	75.13	74.64
Change from baseline5	0.32	-1.04	-1.40
Difference from placebo5 (95% CI)		-1.36** (-2.15, -0.56)	-1.72* (-2.51, -0.93)

a Full analysis set (FAS)

1 LOCF, values after taking antidiabetic rescue therapy censored

2 Mean adjusted for baseline HbA1c, baseline eGFR, geographical region and number of antihypertensive medicinal products

3 LOCF, values after taking antidiabetic rescue therapy or changing antihypertensive rescue therapy censored

4 Mean adjusted for baseline SBP, baseline HbA1c, baseline eGFR, geographical region and number of antihypertensive medicinal products

5 Mean adjusted for baseline DBP, baseline HbA1c, baseline eGFR, geographical region and number of antihypertensive medicinal products

* p-value <0.0001

** p-value <0.001

In a pre-specified pooled analysis of 4 placebo-controlled studies, treatment with empagliflozin (68% of all patients were on metformin background) resulted in a reduction in systolic blood

pressure (empagliflozin 10 mg: -3.9 mmHg, empagliflozin 25 mg: -4.3 mmHg) compared with placebo (-0.5 mmHg), and in diastolic blood pressure (empagliflozin 10 mg: -1.8 mmHg, empagliflozin 25 mg: -2.0 mmHg) compared with placebo (-0.5 mmHg), at week 24, that were maintained up to week 52.

Metformin

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

• a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p=0.0034,

• a significant reduction of the absolute risk of any diabetes-related mortality: metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p=0.017,

• a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years, (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years (p=0.021),

• a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years, (p=0.01).

Paediatric population

5.2 Pharmacokinetic properties

Diajard MXR

The results of bioequivalence studies in healthy subjects demonstrated that Diajard MXR (empagliflozin/metformin hydrochloride) 5 mg/850 mg, 5 mg/1,000 mg, 12.5 mg/850 mg, and 12.5 mg/1,000 mg combination tablets are bioequivalent to co-administration of corresponding doses of empagliflozin and metformin as individual tablets.

Administration of empagliflozin/metformin 12.5 mg/1,000 mg under fed conditions resulted in 9% decrease in AUC and a 28% decrease in Cmax for empagliflozin, when compared to fasted conditions. For metformin, AUC decreased by 12% and Cmax decreased by 26% compared to fasting conditions. The observed effect of food on empagliflozin and metformin is not considered to be clinically relevant. However, as metformin is recommended to be given with meals, Diajard MXR is also proposed to be given with food.

The following statements reflect the pharmacokinetic properties of the individual active substances of Diajard MXR.

Empagliflozin

Absorption

The pharmacokinetics of empagliflozin have been extensively characterised in healthy volunteers and patients with type 2 diabetes. After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median tmax of 1.5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma AUC and Cmax were 1870 nmol.h/l and 259 nmol/l with empagliflozin 10 mg and 4740 nmol.h/l and 687 nmol/l with empagliflozin 25 mg once daily. Systemic exposure of empagliflozin increased in a dose-proportional manner. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar suggesting linear pharmacokinetics with respect to time. There were no clinically relevant differences in empagliflozin pharmacokinetics between healthy volunteers and patients with type 2 diabetes.

The pharmacokinetics of 5 mg empagliflozin twice daily and 10 mg empagliflozin once daily were compared in healthy subjects. Overall exposure (AUCss) of empagliflozin over a 24-hour period with empagliflozin 5 mg administered twice daily was similar to empagliflozin 10 mg administered once daily. As expected, empagliflozin 5 mg administered twice daily compared with 10 mg empagliflozin once daily resulted in lower Cmax and higher trough plasma empagliflozin concentrations (Cmin).

Administration of empagliflozin 25 mg after intake of a high-fat and high calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and Cmax by approximately 37% compared to fasted condition. The observed effect of food on empagliflozin pharmacokinetics was not considered clinically relevant and empagliflozin may be administered with or without food. Similar results were obtained when Diajard MXR (empagliflozin/metformin) combination tablets were administered with high-fat and high calorie meal.

Distribution

The apparent steady-state volume of distribution was estimated to be 73.8 l based on the population pharmacokinetic analysis. Following administration of an oral [14C]-empagliflozin solution to healthy volunteers, the red blood cell partitioning was approximately 37% and plasma protein binding was 86%.

Biotransformation

No major metabolites of empagliflozin were detected in human plasma, as defined by at least 10% of total drug-related material, and the most abundant metabolites were three glucuronide

conjugates (2-, 3-, and 6-O-glucuronide). In vitro studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Elimination

Based on the population pharmacokinetic analysis, the apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 hours and apparent oral clearance was 10.6 l/hour. The inter-subject and residual variabilities for empagliflozin oral clearance were 39.1% and 35.8%, respectively. With once-daily dosing, steady-state plasma concentrations of empagliflozin were reached by the fifth dose. Consistent with the half-life, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state. Following administration of an oral [14C]-empagliflozin solution to healthy volunteers, approximately 96% of the drug-related radioactivity was eliminated in faeces (41%) or urine (54%). The majority of drug-related radioactivity recovered in faeces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

Special populations

Renal impairment

In patients with mild, moderate or severe renal impairment (creatinine clearance <30 - <90 ml/min) and patients with kidney failure/end stage renal disease (ESRD), AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. The population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in creatinine clearance leading to an increase in drug exposure.

Hepatic impairment

In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased approximately by 23%, 47%, and 75% and Cmax by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

Body Mass Index

Body mass index had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis. In this analysis, AUC was estimated to be 5.82%, 10.4%, and 17.3% lower in subjects with BMI of 30, 35, and 45 kg/m2, respectively, compared to subjects with a body mass index of 25 kg/m2.

Gender

Gender had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Race

In the population pharmacokinetic analysis, AUC was estimated to be 13.5% higher in Asians with a body mass index of 25 kg/m2 compared to non-Asians with a body mass index of 25 kg/m2.

Elderly

Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Paediatric population

A paediatric Phase 1 study examined the pharmacokinetics and pharmacodynamics of empagliflozin (5 mg, 10 mg and 25 mg) in children and adolescents ≥10 to <18 years of age with type 2 diabetes mellitus. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects.

Metformin

Absorption

After an oral dose of metformin, tmax is reached in 2.5 hours. Absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride 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 are non-linear. At the recommended metformin doses and dosing schedules, steady-state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 microgram/ml. In controlled clinical trials, maximum metformin plasma levels (Cmax) did not exceed 5 microgram/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg metformin hydrochloride, a 40% lower plasma peak concentration, a 25% decrease in AUC and a 35 minute prolongation of the time to peak plasma concentration were observed. The clinical relevance of these decreases is unknown.

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (Vd) ranged between 63 - 276 l.

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.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Special populations

Paediatric population

Single dose study: after single doses of metformin hydrochloride 500 mg, paediatric patients have shown a similar pharmacokinetic profile to that observed in healthy adults.

Multiple-dose study: After repeated doses of 500 mg twice daily for 7 days in paediatric patients the peak plasma concentration (Cmax) and systemic exposure (AUC0-t) were approximately 33% and 40% lower, respectively, compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

5.3 Preclinical safety data

Empagliflozin and metformin

General toxicity studies in rats of up to 13 weeks were performed with the combination of empagliflozin and metformin and did not reveal any additional target organs when compared to empagliflozin or metformin alone. Some responses were increased by the combination treatment, such as effects on renal physiology, electrolyte balance and acid/base state. However, only hypochloremia was considered adverse at exposures of approximately 9- and 3-times the clinical AUC exposure of the maximum recommended dose of empagliflozin and metformin, respectively.

An embryofetal development study in pregnant rats did not indicate a teratogenic effect attributed to the co-administration of empagliflozin and metformin at exposures of approximately 14-times the clinical AUC exposure of empagliflozin associated with the highest dose, and 4-times the clinical AUC exposure of metformin associated with the 2000 mg dose.

Empagliflozin

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, fertility and early embryonic development.

In long term toxicity studies in rodents and dogs, signs of toxicity were observed at exposures greater than or equal to 10-times the clinical dose of empagliflozin. Most toxicity was consistent with secondary pharmacology related to urinary glucose loss and electrolyte imbalances including decreased body weight and body fat, increased food consumption, diarrhoea, dehydration, decreased serum glucose and increases in other serum parameters reflective of increased protein metabolism and gluconeogenesis, urinary changes such as polyuria and glucosuria, and microscopic changes including mineralisation in kidney and some soft and vascular tissues. Microscopic evidence of the effects of exaggerated pharmacology on the kidney observed in some species included tubular dilatation, and tubular and pelvic mineralisation at approximately 4-times the clinical AUC exposure of empagliflozin associated with the 25 mg dose.

Empagliflozin is not genotoxic.

In a 2-year carcinogenicity study, empagliflozin did not increase the incidence of tumours in female rats up to the highest dose of 700 mg/kg/day, which corresponds to approximately 72-times the maximal clinical AUC exposure to empagliflozin. In male rats, treatment-related benign vascular proliferative lesions (haemangiomas) of the mesenteric lymph node were observed at the highest dose, but not at 300 mg/kg/day, which corresponds to approximately 26-times the maximal clinical exposure to empagliflozin. Interstitial cell tumours in the testes were observed with a higher incidence in rats at 300 mg/kg/day and above, but not at 100 mg/kg/day which corresponds to approximately 18-times the maximal clinical exposure to empagliflozin. Both tumours are common in rats and are unlikely to be relevant to humans.

Empagliflozin did not increase the incidence of tumours in female mice at doses up to 1,000 mg/kg/day, which corresponds to approximately 62-times the maximal clinical exposure to empagliflozin. Empagliflozin induced renal tumours in male mice at 1,000 mg/kg/day, but not at 300 mg/kg/day, which corresponds to approximately 11-times the maximal clinical exposure to empagliflozin. The mode of action for these tumours is dependent on the natural predisposition of the male mouse to renal pathology and a metabolic pathway not reflective of humans. The male mouse renal tumours are considered not relevant to humans.

At exposures sufficiently in excess of exposure in humans after therapeutic doses, empagliflozin had no adverse effects on fertility or early embryonic development. Empagliflozin administered during the period of organogenesis was not teratogenic. Only at maternally toxic doses, empagliflozin also caused bent limb bones in the rat and increased embryofetal loss in the rabbit.

In pre- and postnatal toxicity studies in rats, reduced weight gain of offspring was observed at maternal exposures approximately 4-times the maximal clinical exposure to empagliflozin. No such effect was seen at systemic exposure equal to the maximal clinical exposure to empagliflozin. The relevance of this finding to humans is unclear.

In a juvenile toxicity study in the rat, when empagliflozin was administered from postnatal day 21 until postnatal day 90, non-adverse, minimal to mild renal tubular and pelvic dilation in juvenile

rats was seen only at 100 mg/kg/day, which approximates 11-times the maximum clinical dose of 25 mg. These findings were absent after a 13 weeks drug-free recovery period.

Metformin

Preclinical data for metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, or carcinogenic potential or reproductive toxicity. At dose levels of 500 mg/kg/day administered to Wistar Hannover rats, associated with 7-times the maximum recommended human dose (MRHD) of metformin, teratogenicity of metformin was observed, mostly evident as an increase in the number of skeletal malformations.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients:

Core Tablet
Hydroxypropylcellulose (Klucel EXF)
Microcrystalline Cellulose (Avicel PH 101)
Colloidal Silicon Dioxide (Aerosil - 200)
Hydroxypropylmethylcellulose (HPMC K 100M)
Magnesium Stearate

Film Coating
Hydroxypropylmethylcellulose (Methocel E5)
Polyethylene Glycol 6000 (Macrogol 6000)
Polysorbate 80 (Tween 80)
Talc
Titanium Dioxide
Sunset Yellow Lake E110
Simethicone Emlusion 30%
Purified Water

6.2. Incompatibilities:

Not Applicable

6.3. Shelf-life:

24 months

6.4. Special precautions for storage:

- Store at or below 30°C.
- Protect from heat sunlight and moisture.
- Keep out of the reach of the children.

6.5. Nature and contents of container:

2x7's tablets packed in Alu-Alu blister, in in bleach board unit carton with leaflet.

6.6. Special precautions for disposal:

Not applicable.

7. MANUFACTURER:

Name: Highnoon Laboratories Ltd.
Address: 17.5 km Multan Road, Lahore-53700,
Country: Pakistan
Telephone: +92-42-111000465
E-Mail: info@highnoon.com.pk

8. MARKETING AUTHORIZATION NUMBER:

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION:

10. Date of revision of the text:

Not Applicable

Diajard-MXR 10/1000mg Tablet
(Empagliflozin + Metformin HCl)
(Film Coated Tablet)

Summary of Product characteristics
Ministry of Health
Kenya

HIGHNOON LABORATORIES LIMITED