Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Emjard M 5/500 Tablet

2. Qualitative and quantitative composition

Each Film Coated Tablet Contains Empagliflozin 5 mg & Metformin HCI 500 mg.
Excipients: For a full list of excipients, see section 6.1.

3. Pharmaceutical form

A yellow colored oval biconvex film-coated tablet, engraved 'SQUARE' on one side and bisected on other side.

4. Clinical particulars

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Adults with normal renal function (GFR ≥90 ml/min)

The recommended dose is one tablet twice daily. The dosage should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability using the recommended daily dose of 10 mg or 25 mg of empagliflozin, while not exceeding the maximum recommended daily dose of metformin.

For patients insufficiently controlled on metformin (either alone or in combination with other medicinal products for the treatment of diabetes)

In patients insufficiently controlled on metformin alone or in combination with other medicinal products for the treatment of diabetes, the recommended starting dose of Emjard M Tablet should provide empagliflozin 5 mg twice daily (10 mg daily dose) and the dose of metformin similar to the dose already being taken. In patients tolerating

a total daily dose of empagliflozin 10 mg and who need tighter glycaemic control, the dose can be increased to a total daily dose of empagliflozin 25 mg. When Emjard M Tablet is used in combination with a sulphonylurea and/or insulin, a lower dose of sulphonylurea and/or insulin may be required to reduce the risk of hypoglycemia (see sections 4.5 and 4.8).

For patients switching from separate tablets of empagliflozin and metformin

Patients switching from separate tablets of empagliflozin (10 mg or 25 mg total daily dose) and metformin to Emjard M Tablet should receive the same daily dose of empagliflozin and metformin already being taken or the nearest therapeutically appropriate dose of metformin. (for available strengths see section 2).

Missed dose

If a dose is missed, it should be taken as soon as the patient remembers; however, a double dose should not be taken on the same time. In that case, the missed dose should be skipped.

Special populations

Renal impairment

No dose adjustment is recommended for patients with mild renal impairment. A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

If no adequate strength of Emjard M Tablet is available, individual monocomponents should be used instead of the fixed dose combination.

Table 1: Posology for renally impaired patients

GFR ml/min	**Metformin**	**Empagliflozin**
60-89	Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.	Maximum daily dose is 25 mg.

45-59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	Empagliflozin should not be initiated. The dose should be adjusted to or maintained at a maximum daily dose of 10 mg.
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum	Empagliflozin is not recommended.
	dose.	
<30	Metformin is contraindicated.	Empagliflozin is not recommended.

Hepatic impairment

This medicinal product must not be used in patients with hepatic impairment (see sections 4.3, 4.4 and 5.2).

Elderly

Due to the mechanism of action, decreased renal function will result in reduced glycaemic efficacy of empagliflozin. Because metformin is excreted by the kidney and elderly patients are more likely to have decreased renal function, Emjard M Tablet should be used with caution in these patients. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in elderly patients (see sections 4.3 and 4.4). In patients 75 years and older, an increased risk for volume depletion should be taken into account (see sections 4.4 and 4.8). Due to the limited therapeutic experience with empagliflozin in patients aged 85 years and older, initiation of therapy in this population is not recommended (see section 4.4).

Paediatric population

The safety and efficacy of Emjard M Tablet in children and adolescents aged 0 to 18 years has not been established. No data are available.

Method of administration

Emjard M Tablet should be taken twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin. The tablets should be swallowed whole with water. All patients should continue their diet with an adequate distribution of carbohydrate intake during the day. Overweight patients should continue their energy restricted diet.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis) (see section 4.4).
- Diabetic pre-coma.
- Severe renal failure (GFR <30 ml/min) (see sections 4.2 and 4.4).
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock (see sections 4.4 and 4.8).
- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock (see section 4.4).
- Hepatic impairment, acute alcohol intoxication, alcoholism (see sections 4.2 and 4.5).

4.4 Special warnings and precautions for use

Lactic acidosis

Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections 4.3 and 4.5).

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are

decreased blood pH (<7.35), increased plasma lactate levels (>5 mmol/l) and an increased anion gap and lactate/pyruvate ratio.

Diabetic ketoacidosis

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

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

In patients where DKA is suspected or diagnosed, treatment with empagliflozin should be discontinued immediately.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with empagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilised.

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

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

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

Emjard M Tablet should not be used for treatment of patients with type 1 diabetes. Data from a clinical trial program in patients with type 1 diabetes showed increased DKA occurrence with common frequency in patients treated with empagliflozin 10 mg and 25 mg as an adjunct to

insulin compared to placebo.

Administration of iodinated contrast agent

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see sections 4.2 and 4.5).

Renal function

Due to the mechanism of action, decreased renal function will result in reduced glycaemic efficacy of empagliflozin. GFR should be assessed before treatment initiation and regularly thereafter, see section 4.2. Emjard M Tablet is contraindicated in patients with GFR<30 ml/min and should be temporarily discontinued in the presence of conditions that alter renal function (see section 4.3).

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, Emjard M Tablet may be used with a regular monitoring of cardiac

and renal function. For patients with acute and unstable heart failure, Emjard M Tablet is contraindicated due to the metformin component (see section 4.3).

Surgery

Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Risk for volume depletion

Based on the mode of action of SGLT2 inhibitors, osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in blood pressure (see section 5.1). Therefore, caution should be exercised in patients for whom a empagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or patients aged 75 years and older.

In case of conditions that may lead to fluid loss (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving Emjard M Tablet. Temporary interruption of treatment with Emjard M Tablet should be considered until the fluid loss is corrected.

Elderly

The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the hydration status. Patients aged 75 years and older may be at an increased risk of volume depletion. Therefore, special attention should be given to their volume intake in case of co-administered medicinal products which may lead to volume depletion (e.g. diuretics, ACE inhibitors). Therapeutic experience in patients aged 85 years and older is limited. Initiation of therapy in this population is not recommended (see section 4.2).

Urinary tract infections

Post-marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin (see section 4.8). Temporary interruption of treatment should be considered in patients with complicated urinary tract infections.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Post-marketing cases of necrotising fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients taking SGLT2 inhibitors. This is a rare but serious

and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Emjard M Tablet should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has

been observed in long- term clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot care.

Hepatic injury

Cases of hepatic injury have been reported with empagliflozin in clinical trials. A causal relationship between empagliflozin and hepatic injury has not been established.

Cardiac failure

Experience in New York Heart Association (NYHA) class I-II is limited, and there is no experience in clinical studies with empagliflozin in NYHA class III-IV. In the EMPA-REG OUTCOME study, 10.1% of the patients were reported with cardiac failure at baseline. The reduction of cardiovascular death in these patients was consistent with the overall study population.

Elevated haematocrit

Haematocrit increase was observed with empagliflozin treatment (see section 4.8).

Urine laboratory assessments

Due to its mechanism of action, patients taking Emjard M Tablet will test positive for glucose in their urine.

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

Monitoring glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Use of alternative methods to monitor glycaemic control is advised.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of multiple doses of empagliflozin and metformin does not meaningfully alter the pharmacokinetics of either empagliflozin or metformin in healthy subjects.

No interaction studies have been performed for Emjard M Tablet. The following statements reflect the information available on the individual active substances.

Empagliflozin

Pharmacodynamic interactions

- Diuretics
  Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension (see section 4.4).

- Insulin and insulin secretagogues
  Insulin and insulin secretagogues, such as sulphonylureas, may increase the risk of hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with empagliflozin (see sections 4.2 and 4.8).

Pharmacokinetic interactions

- Effects of other medicinal products on empagliflozin

In vitro data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by uridine 5'-diphosphoglucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Co-administration of empagliflozin with probenecid, an inhibitor of UGT enzymes and OAT3, resulted in a 26% increase in peak empagliflozin plasma concentrations (Cmax) and a 53% increase in area under the concentration-time curve (AUC). These changes were not considered to be clinically meaningful.

The effect of UGT induction (e.g. induction by rifampicin or phenytoin) on empagliflozin has not been studied. Co treatment with known inducers of UGT enzymes is not recommended due to a potential risk of decreased efficacy. If an inducer of these UGT enzymes must be co-administered, monitoring of glycaemic control to assess response to Emjard M Tablet is appropriate.

An interaction study with gemfibrozil, an in vitro inhibitor of OAT3 and OATP1B1/1B3 transporters, showed that empagliflozin Cmax increased by 15% and AUC increased by 59% following co-administration. These changes were not considered to be clinically meaningful.

Inhibition of OATP1B1/1B3 transporters by co-administration with rifampicin resulted in a 75% increase in Cmax and a 35% increase in AUC of empagliflozin. These changes were not considered to be clinically meaningful.

Empagliflozin exposure was similar with and without co-administration with verapamil, a P-gp inhibitor, indicating that inhibition of P-gp does not have any clinically relevant effect on empagliflozin.

Interaction studies suggest that the pharmacokinetics of empagliflozin were not influenced by co- administration with metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, torasemide and hydrochlorothiazide.

- Effects of empagliflozin on other medicinal products

Based on in vitro studies, empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. Drug-drug interactions involving the major CYP450 and UGT isoforms with empagliflozin and concomitantly administered substrates of these enzymes are therefore considered unlikely.

Empagliflozin does not inhibit P-gp at therapeutic doses. Based on in vitro studies, empagliflozin is considered unlikely to cause interactions with active substances that are P-gp substrates. Co- administration of digoxin, a P-gp substrate, with empagliflozin resulted in a 6% increase in AUC and 14% increase in Cmax of digoxin. These changes were not considered to be clinically meaningful.

Empagliflozin does not inhibit human uptake transporters such as OAT3, OATP1B1, and OATP1B3 in vitro at clinically relevant plasma concentrations and, as such, drug-drug interactions with substrates of these uptake transporters are considered unlikely.

Interaction studies conducted in healthy volunteers suggest that empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, simvastatin, warfarin, ramipril, digoxin, diuretics and oral contraceptives.

Metformin

Concomitant use not recommended

Alcohol

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2. Co-administration of metformin with

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin (see sections 4.2 and 4.4).

Iodinated contrast agents

Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see sections 4.2 and 4.4).

Combination requiring precautions for use

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Glucocorticoids (given by systemic and local routes), beta 2 agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be

informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment with such medicinal products. If necessary, the dose of the anti hyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

Insulin and insulin secretagogues

Insulin and insulin secretagogues, such as sulphonylureas, may increase the risk of hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with metformin (see sections 4.2 and 4.8).

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no data from the use of this medicinal product or empagliflozin in pregnant women. Animal studies show that empagliflozin crosses the placenta during late gestation to a very limited extent but do not indicate direct or indirect harmful effects with respect to early embryonic development. However, animal studies have shown adverse effects on postnatal development. A limited amount of data suggests that the use of metformin in pregnant women is not associated with an increased risk of congenital malformations. Animal studies with the combination of empagliflozin and metformin or with metformin alone have shown reproductive toxicity at higher doses of metformin only (see section 5.3).

When the patient plans to become pregnant, and during pregnancy, it is recommended that diabetes is not treated with this medicinal product, but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the foetus associated with abnormal blood glucose levels.

Breast-feeding

Metformin is excreted into human milk. No effects have been shown in breastfed newborns/infants of treated women. No data in humans are available on excretion of empagliflozin into milk. Available animal data have shown excretion of empagliflozin and metformin in milk. A risk to the newborns/infants cannot be excluded.

This medicinal product should not be used during breast feeding.

Fertility

No studies on the effect on human fertility have been conducted for this

medicinal product or empagliflozin. Animal studies with empagliflozin and metformin do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Emjard M Tablet has minor influence on the ability to drive and use machines. Patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines, in particular when Emjard M Tablet is used in combination with a sulphonylurea and/or insulin

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in clinical trials were hypoglycaemia in combination with insulin and/or sulphonylurea, and gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain and loss of appetite) No additional adverse reactions were identified in clinical trials with empagliflozin as add-on to metformin compared to the side effects of the single components.

Tabulated list of adverse reactions

The adverse reactions are listed by absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), or very rare (<1/10,000), and not known (cannot be estimated from the available data).

Table 2: Tabulated list of adverse reactions (MedDRA) from placebo–controlled studies and from post-marketing experience

System organ class	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Infections and infestations		Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection[1], [2] Urinary				Necrotising fasciitis of the perineum (Fournier's gangren

		tract infection (including pyelonephritis and urosepsis) 1, 2				e) a
Metabolism and nutrition disorders	Hypoglycaemia (when used with sulphonylurea or insulin) 1	Thirst 2		Diabetic ketoacidosis a	Lactic acidosis 3 Vitamin B12 deficiency 3, 4	
Nervous system disorders		Taste disturbance 3				
Vascular disorders			Volume depletion 1, 2			
Gastrointestinal disorders	Gastrointestinal symptoms 3, 5					

System organ class	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Hepatobiliary disorders					Liver function tests abnormalities 3 Hepatitis 3	
Skin and subcutaneous tissue disorders		Pruritus (generalised) 2, 3 Rash	Urticaria		Erythema 3	Angioedema

Renal and urinary disorders		Increased urination[1, 2]	Dysuria[2]			
Investigations		Serum lipids increased[2, b]	Blood creatinine increased/ Glomerular filtration rate decreased[1] Haematocrit increased[2, c]			

[1] See subsections below for additional information
[2] Identified adverse reactions of empagliflozin monotherapy
[3] Identified adverse reactions of metformin monotherapy
[4] Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B12 deficiency (e.g. megaloblastic anaemia)
[5] Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.

[a] See section 4.4
[b] Mean percent increases from baseline for empagliflozin 10 mg and 25 mg versus placebo, respectively, were total cholesterol 5.0% and 5.2% versus 3.7%; HDL-cholesterol 4.6% and 2.7% versus -0.5%; LDL-cholesterol 9.1% and 8.7% versus 7.8%; triglycerides 5.4% and 10.8% versus 12.1%.
[c] Mean changes from baseline in haematocrit were 3.6% and 4.0% for empagliflozin 10 mg and 25 mg, respectively, compared to 0% for placebo. In the EMPA-REG Outcome study, haematocrit values returned towards baseline values after a follow-up period of 30 days after

treatment stop.

Description of selected adverse reactions Hypoglycaemia

The frequency of hypoglycaemia depended on the background therapy in the respective studies and was similar for empagliflozin and placebo as add-on to metformin, as add-on to linagliptin and metformin, for the combination of empagliflozin with metformin in drug-naïve patients compared to those treated with empagliflozin and metformin as individual components, and as adjunct to standard care therapy. An increased frequency was noted when empagliflozin given as add-on to metformin and a sulfonylurea (empagliflozin 10 mg: 16.1%, empagliflozin 25 mg: 11.5% and placebo: 8.4%), or as add-on to metformin and insulin (empagliflozin 10 mg: 31.3%, empagliflozin 25 mg: 36.2% and placebo: 34.7%).

Major hypoglycaemia (events requiring assistance)

The overall frequency of patients with major hypoglycaemic events was low (<1%) and similar for empagliflozin and placebo as add-on to metformin, and for the combination of empagliflozin with metformin in drug-naïve patients compared to those treated with empagliflozin and metformin as individual components, and as adjunct to standard care therapy. Major hypoglycaemic events occurred in 0.5%, 0% and 0.5% of patients treated with empagliflozin 10 mg, empagliflozin 25 mg and placebo when added on to metformin and insulin, respectively. No patient had a major hypoglycaemic event in the combination with metformin and a sulphonylurea and as add-on to linagliptin and metformin.

Urinary tract infection

The overall frequency of urinary tract infection adverse events was higher in metformin-treated patients who received empagliflozin 10 mg (8.8%) compared to empagliflozin 25 mg (6.6%) or placebo (7.8%). Similar to placebo, urinary tract infection was reported more frequently for empagliflozin in patients with a history of chronic or recurrent urinary tract infections. The intensity of urinary tract infections (i.e. mild/moderate/severe) was similar to placebo. Urinary tract infection events were reported more frequently for empagliflozin 10 mg compared with placebo in female patients, but not for empagliflozin 25 mg. The frequencies of urinary tract infections were low for male patients and were balanced across treatment groups.

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently in metformin-treated patients who received empagliflozin 10 mg (4.0%) and empagliflozin 25 mg (3.9%) compared to placebo (1.3%), and were reported more frequently for empagliflozin compared to placebo in female patients. The difference in frequency was less pronounced in male patients. Genital tract infections were mild and moderate in intensity, none was severe in intensity.

Increased urination

As expected from the mechanism of action, increased urination (as assessed by PT search including pollakiuria, polyuria, nocturia) was observed at higher frequencies in metformin-treated patients who received empagliflozin 10 mg (3.0%) and empagliflozin 25 mg (2.9%) compared to placebo (1.4%) as

add-on to metformin therapy. Increased urination was mostly mild or moderate in intensity. The frequency of reported nocturia was comparable between placebo and empagliflozin (<1%).

Volume depletion

The overall frequency of volume depletion (including the predefined terms blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolaemia, orthostatic hypotension, and syncope) in metformin-treated patients who received empagliflozin was low: 0.6% for empagliflozin 10 mg, 0.3% for empagliflozin 25 mg and 0.1% for placebo. The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect hydration status of patients age 75 years and older. In patients ≥75 years of age volume depletion events have been reported in a single patient treated with empagliflozin 25 mg as add-on to metformin therapy.

Blood creatinine increased/Glomerular filtration rate decreased

The overall frequency of patients with increased blood creatinine and decreased glomerular filtration rate were similar between empagliflozin and placebo as add-on to metformin (blood creatinine increased: empagliflozin 10 mg 0.5%, empagliflozin 25 mg 0.1%, placebo 0.4%; glomerular filtration
rate decreased: empagliflozin 10 mg 0.1%, empagliflozin 25 mg 0%, placebo 0.2%).

Initial increases in creatinine and initial decreases in estimated

glomerular filtration rates in patients treated with empagliflozin as add-on to metformin therapy were generally transient during continuous treatment or reversible after drug discontinuation of treatment.

Consistently, in the EMPA-REG OUTCOME study, patients treated with empagliflozin experienced an initial fall in eGFR (mean: 3 ml/min/1.73 m2). Thereafter, eGFR was maintained during continued treatment. Mean eGFR returned to baseline after treatment discontinuation suggesting acute haemodynamic changes may play a role in these renal function changes.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Symptoms

Empagliflozin

In controlled clinical studies single doses of up to 800 mg empagliflozin (equivalent to 32-times the highest recommended daily dose) in healthy volunteers and multiple daily doses of up to 100 mg empagliflozin (equivalent to 4-times the highest recommended daily dose) in patients with type 2 diabetes did not show any toxicity. Empagliflozin increased urine glucose excretion leading to an increase in urine volume. The observed increase in urine volume was not dose-dependent and is not clinically meaningful. There is no experience with doses above 800 mg in humans.

Metformin

Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin or concomitant risks may lead to lactic

acidosis. Lactic acidosis is a medical emergency and must be treated in hospital (see sections 4.4 and 4.5).

Therapy

In the event of an overdose, treatment should be initiated as appropriate to the patient's clinical status. The most effective method to remove lactate and metformin is haemodialysis. The removal of empagliflozin by haemodialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD20

Mechanism of action

Emjard M Tablet 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 therapy[a]			
	Placebo	**Empagliflozin**	
		10 mg	**25 mg**
N	207	217	213
HbA1c (%)			
Baseline (mean)	7.90	7.94	7.86
Change from baseline[1]	-0.13	-0.70	-0.77
Difference from placebo[1] (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 baseline[1]	-0.45	-2.08	-2.46
Difference from placebo[1] (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 baseline[1]	-0.4	-4.5	-5.2
Difference from placebo[1] (95% CI)		-4.1* (-6.2, -2.1)	-4.8* (-6.9, -2.7)

Add-on to metformin and a sulphonylurea therapy[a]			
	Placebo	**Empagliflozin**	
		10 mg	**25 mg**
N	225	225	216
HbA1c (%)			

Add-on to metformin therapy[a]			
	Placebo	**Empagliflozin**	
		10 mg	**25 mg**
Baseline (mean)	8.15	8.07	8.10
Change from baseline[1]	-0.17	-0.82	-0.77
Difference from placebo[1] (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 baseline[1]	-0.39	-2.16	-2.39
Difference from placebo[1] (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 baseline[1]	-1.4	-4.1	-3.5
Difference from placebo[1] (95% CI)		-2.7 (-4.6, -0.8)	-2.1 (-4.0, -0.2)

Add-on to pioglitazone + metformin therapy[b]			
	Placebo	**Empagliflozin**	
		10 mg	**25 mg**
N	124	125	127
HbA1c (%)			
Baseline (mean)	8.15	8.07	8.10
Change from baseline[1]	-0.11	-0.55	-0.70
Difference from placebo[1]		-0.45* (-0.69, -	-0.60* (-0.83, -

(97.5% CI)		0.21)	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 baseline[1]	0.40	-1.74	-1.59
Difference from placebo[1] (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

Add-on to metformin therapy[a]			
	Placebo	**Empagliflozin**	
		10 mg	**25 mg**
Change from baseline[1]	0.8	-3.5	-3.3
Difference from placebo[1] (95% CI)		-4.2** (-6.94, -1.53)	-4.1** (-6.76, -1.37)

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[b]			**Empagliflozin 25 mg[b]**			**Metformin[c]**	
	+ Met 1000 mg[c]	+ Met 2000 mg[c]	No Met	+ Met 1000 mg[c]	+ Met 2000 mg[c]	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 baseline 1	-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			
	Placebo[5]	**Empagliflozin[6]**	
		10 mg	**25 mg**
N	106	109	110

HbA1c (%)[3]			
Baseline (mean)	7.96	7.97	7.97
Change from baseline[1]	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 baseline[1]	-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 baseline[1]	-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 metformin[a]

	Empagliflozin 25 mg	**Glimepiride[b]**
N	765	780
HbA1c (%)		
Baseline (mean)	7.92	7.92
Change from baseline[1]	-0.66	-0.55
Difference from glimepiride[1] (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 baseline[1]	-3.12	1.34

	Empagliflozin 25 mg	**Glimepiride[b]**
Difference from glimepiride[1] (97.5% CI)	-4.46** (-4.87, -4.05)	
N	765	780
SBP (mmHg)[3]		
Baseline (mean)	133.4	133.5
Change from baseline[1]	-3.1	2.5
Difference from glimepiride[1] (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 18[a]			
Baseline (mean)	8.29	8.42	8.29
Change from baseline[1]	-0.58	-0.99	-1.03

	Placebo	**empagliflozin**	
		10 mg	**25 mg**
Difference from placebo[1] (97.5% CI)		-0.41* (-0.61, -0.21)	-0.45* (-0.65, -0.25)
N	86	84	87
HbA1c (%) at week 52[b]			
Baseline (mean)	8.26	8.43	8.38
Change from baseline[1]	-0.86	-1.23	-1.31

Difference from placebo[1] (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 52[b, 2]	27.4	41.7	48.3
N	86	83	86
Insulin dose (IU/day) at week 52[b, 3]			
Baseline (mean)	91.01	91.77	90.22
Change from baseline[1]	12.84	0.22	-2.25
Difference from placebo[1] (97.5% CI)		-12.61** (-21.43, -3.80)	-15.09** (-23.79, -6.40)
N	86	84	87
Body Weight (kg) at week 52[b]			
Baseline (mean)	97.78	98.86	94.93
Change from baseline[1]	0.42	-2.47	-1.94
Difference from placebo[1] (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 baseline[1]	-0.09	-0.62	-0.72
Difference from placebo[1] (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 baseline[1]	-0.08	-0.42	-0.71
Difference from placebo[1] (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 baseline[1]	4.14	-2.07	-0.28
Difference from placebo[1] (97.5% CI)		-6.21** (-11.81, -0.61)	-4.42 (-10.18, 1.3

[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

<u>Empagliflozin and linagliptin as add-on therapy to metformin</u>

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 mortality [a]

	Placebo	**Empagliflozin[b]**
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.

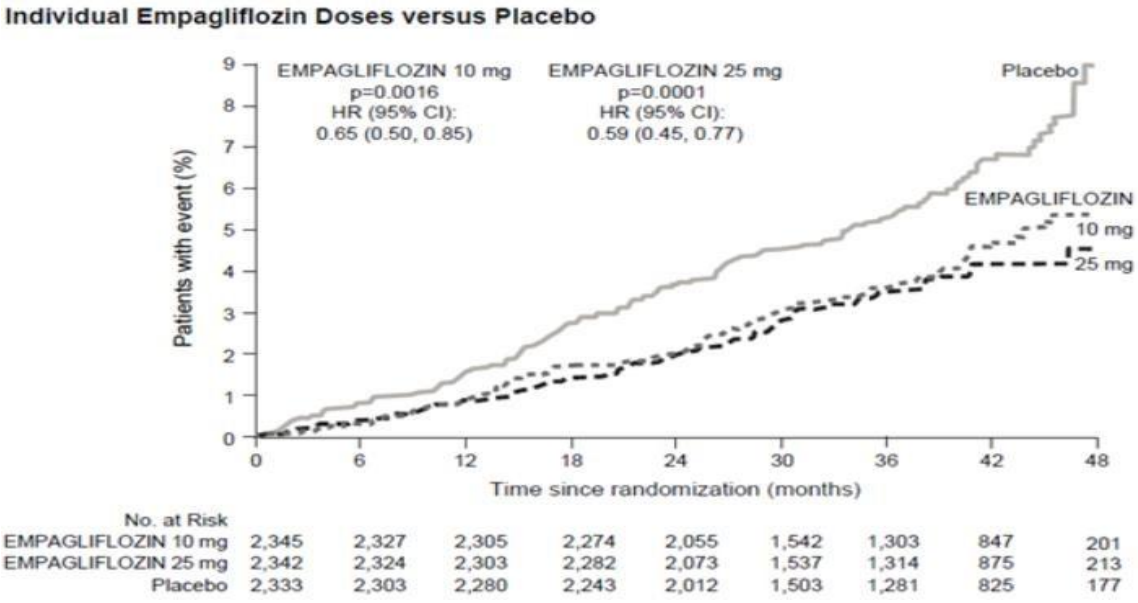

Figure 1 Time to occurrence of cardiovascular death in the EMPA-REG OUTCOME study

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 pressure [a]

		empagliflozin	
	Placebo	**10 mg**	**25 mg**
N	271	276	276
HbA1c (%) at week 12[1]			
Baseline (mean)	7.90	7.87	7.92
Change from baseline[2]	0.03	-0.59	-0.62
Difference from placebo[1] (95% CI)[2]		-0.62* (-0.72, -0.52)	-0.65* (-0.75, -0.55)
24 hour SBP at week 12[3]			
Baseline (mean)	131.72	131.34	131.18
Change from baseline[4]	0.48	-2.95	-3.68
Difference from placebo[4] (95% CI)		-3.44* (-4.78, -2.09)	-4.16* (-5.50, -2.83)
24 hour DBP at week 12[3]			
Baseline (mean)	75.16	75.13	74.64
Change from baseline[5]	0.32	-1.04	-1.40
Difference from placebo[5] (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

The European Medicines Agency has waived the obligation to submit the results of studies with Emjard M Tablet in all subsets of the paediatric population in type 2 diabetes (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The results of bioequivalence studies in healthy subjects demonstrated that Emjard M Tablet (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, Emjard M Tablet is also proposed to be given with food.

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 Emjard M Tablet (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

- Pre-gelatinized Starch
- Co-povidone
- Colloidal Anhydrous Silica
- Magnesium Stearate

- Opadry II 85G520064 Yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 30°C, keep away from light & moisture. Keep out of the reach of the children

6.5 Nature and contents of container

Alu-Alu blister pack.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. Market authorization holder

Square Pharmaceuticals Ltd**.**
Square Centre
48, Mohakhali C.A, Dhaka –
1212, Bangladesh
Tel: +880 2 8833047-56, +880 2 8859007 (10 lines)
Fax: +880 2 8828768, +880 2 8834941
E-mail: info@squaregroup.com

8. Marketing authorization number:

CTD10992

9. Date of first authorization

21 Nov 2024

10. Date of revision of the text

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