Summary of Product Characteristics
EMPAGOOD M
(FIXED DOSE COMBINATION OF EMPAGLIFLOZIN 12.5 MG AND METFORMIN HCL 500MG TABLETS)

1. Name of the medicinal product
EMPAGOOD M
(Fixed Dose Combination of Empagliflozin 12.5 mg and Metformin HCL 500mg Tablets)

2. Qualitative and Quantitative composition
Each Tablet contains 12.5 mg Empagliflozin, 500mg Metformin hydrochloride USP.

Excipients of Known effects:
Refer to section 6.1 for the full list of excipients.

3. Pharmaceutical form
Tablets
A Light Brick red colored, elongated, biconcave, film coated tablet.

4. CLINICAL PARTICULARS:
4.1 Therapeutic indications
EMPAGOOD M is indicated for the treatment of adults with type 2 diabetes mellitus as an adjunct to diet and exercise:
- in patients insufficiently controlled on their maximally tolerated dose of metformin alone
- in combination with other medicinal products for the treatment of diabetes, in patients insufficiently controlled with metformin and these medicinal products
- in patients already being treated with the combination of empagliflozin and metformin as separate tablets.

For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the population studied.

4.2 Posology and method of administration
Posology
Adults with normal renal function (eGFR ≥90 ml/min/1.73 m2)
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 EMPAGOOD M 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 EMPAGOOD M 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

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EMPAGOOD M
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Patients switching from separate tablets of empagliflozin (10 mg or 25 mg total daily dose) and metformin to EMPAGOOD M should receive the same daily dose of empagliflozin and metformin already being taken or the nearest therapeutically appropriate dose of metformin

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

The glycaemic efficacy of empagliflozin is dependent on renal function. For cardiovascular risk reduction as add on to standard of care, a dose of 10 mg empagliflozin daily should be used in patients with an eGFR below 60 ml/min/1.73 m2 (see Table 1). Because the glycaemic lowering efficacy of empagliflozin is reduced in patients with moderate renal impairment and likely absent in patients with 4 severe renal impairment, if further glycaemic control is needed, the addition of other antihyperglycaemic agents should be considered. For dose adjustment recommendations according to eGFR or CrCL refer to Table 1.

A eGFR 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 EMPAGOOD M is available, individual monocomponents should be used instead of the fixed dose combination.

Table 1: Posology for renally impaired patients

eGFR [ml/min/1.73 m²] or CrCL [ml/min] ≥60 45 to <60 30 to <45 <30 Metformin Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function. Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose. Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose. Metformin is contraindicated. Empagliflozin Initiate with 10 mg. In patients tolerating 10 mg and requiring additional glycaemic control, the dose can be increased to 25 mg. Initiate with 10 mg. b Continue with 10 mg in patients already taking empagliflozin. Initiate with 10 mg. b Continue with 10 mg in patients already taking empagliflozin.b Empagliflozin is not recommended.

Egfr [ml/min/1.73 m^2] or CrCL [ml/min]	**Metformin**	**Empagliflozin**
≥60	Metformin Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function	Initiate with 10 mg. In patients tolerating 10 mg and requiring additional glycaemic control, the dose can be increased to 25 mg.
45 to <60	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose. Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	Initiate with 10 mg. [b] Continue with 10 mg in patients already taking empagliflozin

30 to <45	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	Initiate with 10 mg. [b] Continue with 10 mg in patients already taking empagliflozin.[b]
<30	Metformin is contraindicated.	Empagliflozin is not recommended.

Hepatic impairment
This medicinal product must not be used in patients with hepatic impairment

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, EMPAGOOD M 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. In patients 75 years and older, an increased risk for volume depletion should be taken into account,

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

Method of administration
EMPAGOOD M 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.

Method of administration
Oral

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)
- Diabetic pre-coma.
- Severe renal failure (eGFR <30 ml/min/1.73 m2)
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock
- 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
- Hepatic impairment, acute alcohol intoxication, alcoholism

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

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 (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.

EMPAGOOD M should not be used in 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.

Renal impairment

Due to the mechanism of action, decreased renal function will result in reduced glycaemic efficacy of empagliflozin. Empagliflozin/metformin is contraindicated in patients with eGFR<30 ml/min/1.73 m2 and should be temporarily discontinued in the presence of conditions that alter renal function
Monitoring of renal function
Assessment of renal function is recommended as follows: - Prior to empagliflozin/metformin initiation and periodically during treatment, i.e. at least yearly - Prior to initiation of any concomitant medicinal product that may have a negative impact on renal function.
Cardiac function
Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, EMPAGOOD M may be used with a regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, EMPAGOOD M is contraindicated due to the metformin component
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. Therefore, caution 7 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 EMPAGOOD M. Temporary interruption of treatment with EMPAGOOD M 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 coadministered medicinal products which may lead to volume depletion (e.g. diuretics, ACE inhibitors).
Urinary tract infections
Post marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin . Temporary interruption of treatment should be considered in patients with complicated urinary tract infections.

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 EMPAGOOD M.
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

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.

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 9 risk of decreased efficacy. If an inducer of these UGT enzymes must be co-administered, monitoring of glycaemic control to assess response to EMPAGOOD M 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 Empagliflozin may increase renal lithium excretion and the blood lithium levels may be decreased. Serum concentration of lithium should be monitored more frequently after empagliflozin initiation and dose changes. Please refer the patient to the lithium prescribing doctor in order to monitor serum concentration of lithium.

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. 10
• 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 coadministered 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.
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.
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

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.
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

4.7 Effects on ability to drive and use machines
EMPAGOOD M 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 EMPAGOOD M 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), not known (cannot be estimated from the available data).

post-marketing experience Table 2: Tabulated list of adverse reactions (MedDRA) from placebo-controlled studies and from System organ class Very common Common Uncommon Rare Very rare Infections and infestations Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection Urinary tract infection (including pyelonephritis and urosepsis)-2 Necrotising fasciitis of the perineum (Fournier's gangrene) Metabolism and mutrition disorders Hypoglycaemia (when used with sulphonylurea or insulin) Thirst Vitamin B12 decrease/deficiency Diabetic ketoacidosis Lactic

acidosis Nervous system disorders Taste disturbance Volume depletion Vascular disorders Gastrointestinal disorders Gastrointestinal symptoms Constipation Hepatobiliary disorders Skin and subcutaneous tissue disorders Renal and urinary disorders Investigations Pruritis (generalised) Rash Increased urination Serum lipids increased Urticaria Angioedema Dysuria Blood creatinine increased Glomerular filtration rale decreased Haematocrit increased Liver function tests abnormalities Hepatitis 1 Erythema Tubulointerstitial nephritis

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**
Infections and infestations		Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection [1-2] Urinary tract infection (including pyelonephritis and urosepsis)[1-2]		Necrotising fasciitis of the perineum (Fournier's gangrene)[a]	
Metabolism and mutrition disorders	Hypoglycaemia (when used with sulphonylurea or insulin)[1]	Thirst[2] Vitamin B12 decrease/deficiency [3,a]		Diabetic ketoacidosis[a]	Lactic acidosis[3]
Nervous system disorders		Taste disturbance[3]			
Vascular disorders			Volume depletion [1,2,d]		
Gastrointestinal disorders	Gastrointestinal symptoms [3,4]	Constipation			
Hepatobiliary disorders					Liver function tests abnormalities [3] Hepatitis[3]
Skin and subcutaneous tissue disorders		Pruritis (generalised)[2,3] Rash	Urticaria Angioedema		Erythema[3]

Renal and urinary disorders Investigations		Increased urination [1,2]	Dysuria[2]		Tubulointerstitial nephritis
Investigations		Serum lipids increased [2,b]	Blood creatinine increased Glomerular filtration rale decreased Haematocrit increased [2,e]		

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to National Regulatory Agents

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.
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
Pharmacodynamic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs,
ATC Code: A10BD20
Mechanism of action

Summary of Product Characteristics
EMPAGOOD M
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EMPAGOOD M 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.

5.2 Pharmacokinetic properties

EMPAGOOD M

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

The following statements reflect the pharmacokinetic properties of the individual active substances of EMPAGOOD M.

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 EMPAGOOD M (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.

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 30 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

Microcrystalline Cellulose
Maize Starch
Methylparaben sodium
Propylparaben sodium
Povidone K-30
Purified water
Purified talc
Magnesium Stearate
Cross carmelose sodium
Colloidal Silicon Dioxide
Ready coat Brown
Isopropyl Alcohol
Methylene Chloride

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at the temperature not exceeding 30°C. Protect from light.

6.5 Nature and contents of container

10 tablets are packed in one Alu-Alu blister such 3 blisters are packed in a carton with insert. Pack such cartons in shipper box. Seal shipper box with BOPP tape. Affix one label on each shipper box

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

Summary of Product Characteristics
EMPAGOOD M
(FIXED DOSE COMBINATION OF EMPAGLIFLOZIN 12.5 MG AND METFORMIN HCL 500MG TABLETS)

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURER

Marketing Authorisation Holder:
ZAIN PHARMA LTD.
Plot No: 209/13741, Colchester Park,
Go-Down No.1, 2, 3, Off Mombasa Road,
Behind Nice And Lovely House,
P.O. Box: 100167-00101, Nairobi, Kenya

8. Marketing Authorization Number:

CTD11597

9. Date of First <Registration> / Renewal of The <Registration>

8th May 2026

10. Date of Revision of the Text: