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Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Glifempa XR 10 mg /1000 mg Extended-Release Tablets

2. Qualitative and quantitative composition

Each Uncoated bilayered tablet contains:

Empagliflozin 10 mg

Metformin Hydrochloride BP 1000 mg

(As Extended Release)

Excipients Q.S.

Colour: Tartrazine FCF & Titanium Dioxide BP

Excipients with known effect

Mannitol

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Uncoated tablet

White and Yellow coloured elongated shape, biconvex, scored on yellow side, plain on other side uncoated bilayered Tablets.

4. Clinical particulars

4.1 Therapeutic indications

GLIFEMPA XR is a combination of empagliflozin and metformin hydrochloride (HCl) indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease.

Limitation of Use

GLIFEMPA XR is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

4.2 Posology and method of administration

-Assess renal function before initiating and as clinically indicated.

Individualize the starting dose of glifempa xr based on the patient's current regimen:

-In patients on metformin hcl, switch to glifempa xr containing a similar total daily dose of metformin hcl and a total daily dose of empagliflozin 10 mg;

-In patients on empagliflozin, switch to glifempa xr containing the same total daily dose of empagliflozin and a total daily dose of metformin hcl extended-release 1000 mg;

-In patients already treated with empagliflozin and metformin HCL, switch to glifempa xr containing the same total daily doses of empagliflozin and a similar total daily dose of metformin hcl.

Monitor effectiveness and tolerability, and adjust dosing as appropriate, not to exceed the maximum recommended daily dose of empagliflozin 25 mg and metformin hcl 2000 mg.

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

Take glifempa xr orally once daily with a meal in the morning

Swallow glifempa xr tablets whole. Do not split, crush, dissolve, or chew.

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

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, it 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).

Paediatric population

The dosage should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability.

If empagliflozin is added in patients already receiving metformin, the metformin dose should remain the same as the patient is already taking. The recommended empagliflozin starting dose is 5 mg twice daily (10 mg total daily doses). In patients tolerating empagliflozin 5 mg twice daily and requiring additional glycaemic control, the dose can be increased to 12.5 mg twice daily (25 mg total daily dose).

No data are available for children with eGFR <60 ml/min/1.73 m^2 and children below 10 years of age.

Dosage Recommendations in Patients with Renal Impairment

Initiation of GLIFEMPA XR is not recommended in patients with an eGFR less than 45 mL/min/1.73 m^2, due to the metformin component.

GLIFEMPA XR is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 or in patients on dialysis.

Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue glifempa xr at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart glifempa xr if renal function is stable.

Method of administration

Glifempa xr 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

GLIFEMPA XR is contraindicated in patients with:

- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end stage renal disease, or dialysis.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis.
- Hypersensitivity to empagliflozin, metformin or any of the excipients in glifempa xr, reactions such as angioedema have occurred.
- 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

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

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of glifempa xr. In glifempa XR-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin is dialyzable, with clearance of up to 170 mL/minute under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue glifempa xr and report these symptoms to their healthcare provider.

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

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

Before initiating glifempa xr, obtain an estimated glomerular filtration rate (eGFR).

GLIFEMPA XR is contraindicated in patients with an eGFR below 30

mL/min/1.73 m^2.
Obtain an eGFR at least annually in all patients taking glifempa xr. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
Drug interactions: the concomitant use of glifempa xr with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation.
Therefore, consider more frequent monitoring of patients.
Age 65 or Greater: The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.
Radiological Studies with Contrast: Administration of intravascular iodinated contrast agents in metformin- treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop glifempa xr at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 60 mL/min/1.73 m^2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart glifempa xr if renal function is stable.
Surgery and other procedures: withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. Glifempa xr should be temporarily discontinued while patients have restricted food and fluid intake.
Hypoxic States: Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue glifempa xr.
Excessive alcohol intake: alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving glifempa xr.
Hepatic impairment: patients with hepatic impairment have developed cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of glifempa xr in patients with clinical or laboratory evidence of hepatic disease.

Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in clinical trials and postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including empagliflozin. Fatal cases of ketoacidosis have been reported in patients taking empagliflozin. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. Glifempa xr is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with empagliflozin and metformin extended-release tablets who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with empagliflozin and metformin extended-release tablets may be present

even if blood glucose levels are less than 250 mg/dl. If ketoacidosis is suspected, empagliflozin and metformin extended-release tablets should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.
In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.
Before initiating empagliflozin and metformin extended release tablets, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.
For patients who undergo scheduled surgery, consider temporarily discontinuing empagliflozin and metformin extended release tablets for at least 3 days prior to surgery.
Consider monitoring for ketoacidosis and temporarily discontinuing empagliflozin and metformin extended-release tablets in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting empagliflozin and metformin extended-release tablets.
Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue empagliflozin and metformin extended-release tablets and seek medical attention immediately if signs and symptoms occur.

Volume Depletion

Empagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating empagliflozin and metformin extended release tablets in patients with one or more of these characteristics, assess volume status and renal function. in patients with volume depletion, correct this condition before initiating empagliflozin and metformin extended-release tablets. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.

Urosepsis and Pyelonephritis

There have been post marketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including empagliflozin.

Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when empagliflozin is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin. Metformin may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with empagliflozin and metformin extended release tablets.

Necrotizing fasciitis of the perineum (fournier's gangrene)

Reports of necrotizing fasciitis of the perineum (fournier's gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving sglt2 inhibitors, including empagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with empagliflozin and metformin extended release tablets

Presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad- spectrum antibiotics and, if necessary, surgical debridement. Discontinue empagliflozin and metformin extended release tablets, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections

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

Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions, (e.g., angioedema) in patients treated with empagliflozin. If a hypersensitivity reaction occurs, discontinue empagliflozin and metformin extended release tablets; treat promptly per standard of care, and monitor until signs and symptoms resolve. Empagliflozin and metformin extended release tablets is contraindicated in patients with hypersensitivity to empagliflozin or any of the excipients in empagliflozin and metformin extended release tablets.

Vitamin B12 Deficiency

In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. Measure hematologic parameters on an annual basis and vitamin b12 at 2 to 3 year intervals in patients on empagliflozin and metformin extended release tablets and manage any abnormalities.

4.5 Interaction with other medicinal products and other forms of interaction

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Carbonic Anhydrase Inhibitors	
Clinical Impact	Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis.
Intervention	Concomitant use of these drugs with GLIFEMPA XR may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients.
Drugs that Reduce Metformin Clearance	
Clinical Impact	Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis.
Intervention	Consider the benefits and risks of concomitant use.
Alcohol	
Clinical Impact	Alcohol is known to potentiate the effect of metformin on lactate metabolism.
Intervention	Warn patients against excessive alcohol intake while receiving GLIFEMPA XR.
Diuretics	
Clinical Impact	Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
Intervention	Before initiating GLIFEMPA XR, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating GLIFEMPA XR. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.
Insulin or Insulin Secretagogues	
Clinical Impact	The risk of hypoglycemia is increased when empagliflozin is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin. Metformin may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue.
Intervention	Coadministration of GLIFEMPA XR with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
Drugs Affecting Glycemic Control	
Clinical Impact	Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid.

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Intervention	When such drugs are administered to a patient receiving GLIFEMPA XR, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving GLIFEMPA XR, the patient should be observed closely for hypoglycemia.

Positive Urine Glucose Test	
Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
Intervention	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
Clinical Impact	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
Intervention	Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control.

Table 4 clinically relevant interactions with empagliflozin and metformin extended release tablets

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk summary

Based on animal data showing adverse renal effects from empagliflozin, empagliflozin and metformin extended release tablets is not recommended during the second and third trimesters of pregnancy.

The limited available data with empagliflozin and metformin extended release tablets or empagliflozin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy.

In animal studies, empagliflozin, a component of empagliflozin and metformin extended release tablets, resulted in adverse renal changes in rats when administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 13-times the maximum clinical dose caused renal pelvic and tubule dilatations that were reversible. No adverse developmental effects were observed when metformin was administered to pregnant rats or rabbits. The estimated background risk of major birth defects is 6% to 10% in women with pre-gestational diabetes with a hba1c >7 and has been reported to be as high as 20% to 25% in women with hba1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the u.s. General population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical considerations

Disease-associated maternal and/or embryo/fetal risk: poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled

diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Human data

Published data from postmarketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during Pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal data

Empagliflozin: empagliflozin dosed directly to juvenile rats from postnatal day (pnd) 21 until pnd 90 at doses of 1, 10, 30, and 100 mg/kg/day caused increased kidney weights and renal tubular and pelvic dilatation at 100 mg/kg/day, which approximates 13-times the maximum clinical dose of 25 mg, based on auc. These findings were not observed after a 13-week, drug-free recovery period. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development.

In embryo-fetal development studies in rats and rabbits, empagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. Doses up to 300 mg/kg/day, which approximates 48-times (rats) and 128-times (rabbits) the maximum clinical dose of 25 mg (based on auc), did not result in adverse developmental effects. In rats, at higher doses of empagliflozin causing maternal toxicity, malformations of limb bones increased in fetuses at 700 mg/kg/day or 154-times the 25 mg maximum clinical dose. Empagliflozin crosses the placenta and reaches fetal tissues in rats. In the rabbit, higher doses of empagliflozin resulted in maternal and fetal toxicity at 700 mg/kg/day, or 139-times the 25 mg maximum clinical dose.

In pre- and postnatal development studies in pregnant rats, empagliflozin was administered from gestation day 6 through to lactation day 20 (weaning) at up to 100 mg/kg/day (approximately 16-times the 25 mg maximum clinical dose) without maternal toxicity. Reduced body weight was observed in the offspring at greater than or equal to 30 mg/kg/day (approximately 4-times the 25 mg maximum clinical dose).

Metformin hydrochloride: metformin hydrochloride did not cause adverse developmental effects when administered to pregnant sprague dawley rats and rabbits at up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of approximately 2- and 6-times a clinical dose of 2000 mg, based on body surface area (mg/m^2) for rats and rabbits, respectively.

Empagliflozin and metformin hydrochloride: no adverse developmental effects were observed when empagliflozin and metformin hydrochloride were coadministered to pregnant rats during the period of organogenesis at exposures of approximately 35- and 14-times the clinical auc exposure of empagliflozin associated with the 10 mg and 25 mg doses, respectively, and 4-times the clinical auc exposure of metformin associated with the 2000 mg dose.

Lactation

Risk summary

There is limited information regarding the presence of empagliflozin and metformin extended release tablets or its components (empagliflozin or metformin) in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that metformin is present in human milk. Empagliflozin is present in the

milk of lactating rats. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.
Because of the potential for serious adverse reactions in a breastfed infant, including the potential for empagliflozin to affect postnatal renal development, advise patients that use of empagliflozin and metformin extended release tablets is not recommended while breastfeeding.
Data
Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging

Between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants. Empagliflozin was present at a low level in rat fetal tissues after a single oral dose to the dams at gestation day 18. In rat milk, the mean milk to plasma ratio ranged from 0.634 to 5, and was greater than one from 2 to 24 hours post-dose. The mean maximal milk to plasma ratio of 5 occurred at 8 hours post-dose, suggesting accumulation of empagliflozin in the milk. Juvenile rats directly exposed to empagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

4.7 Effects on ability to drive and use machines

Empagliflozin and metformin extended release tablets 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 empagliflozin and metformin extended release tablets is used in combination with a sulphonylurea and/or insulin.

4.8 Undesirable effects

The following important adverse reactions are described below and elsewhere in the labeling:
-lactic acidosis
-ketoacidosis
-volume depletion
-urosepsis and pyelonephritis
-hypoglycemia with concomitant use with insulin and insulin secretagogues
-necrotizing fasciitis of the perineum (fournier's gangrene)
-genital mycotic infections
-hypersensitivity reactions
-vitamin b12 deficiency

Clinical trials experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The safety of concomitantly administered empagliflozin (daily dose 10 mg and 25 mg) and metformin hydrochloride (mean daily dose of approximately 1800 mg) has been evaluated in 3456 patients with type 2 diabetes mellitus treated for 16 to 24 weeks, of which 926 patients received placebo, 1271 patients received a daily dose of empagliflozin 10 mg, and 1259 patients received a daily dose of empagliflozin 25 mg.

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Discontinuation of therapy due to adverse events across treatment groups was 3.0%, 2.8%, and 2.9% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Empagliflozin add-on combination therapy with metformin

In a 24-week placebo-controlled trial of empagliflozin 10 mg and 25 mg administered once daily added to metformin, there were no adverse reactions reported regardless of investigator assessment of causality in
≥5% of patients and more commonly than in patients given placebo.

Empagliflozin add-on combination therapy with metformin and sulfonylurea

In a 24-week placebo-controlled trial of empagliflozin 10 mg and 25 mg administered once daily added to metformin and sulfonylurea, adverse reactions reported regardless of investigator assessment of causality in
≥5% of patients and more commonly than in patients given placebo are presented in table 1 (see also table 4).

Adverse reactions	**Placebo (%) n=225**	**Empagliflozin 10 mg (%) n=224**	**Empagliflozin 25 mg (%) n=217**
Hypoglycemia	9.8	15.6	12.9
Urinary tract infection	6.7	9.4	6.9
Nasopharyngitis	4.9	8.0	6.0

Table 1 adverse reactions reported in ≥5% of patients treated with empagliflozin added on to metformin plus sulfonylurea and greater than with placebo in a 24-week placebo controlled clinical study

Empagliflozin

The data in table 2 are derived from a pool of four 24-week placebo-controlled trials and 18-week data from a placebo-controlled trial with basal insulin. Empagliflozin was used as monotherapy in one trial and as add- on therapy in four trials.
These data reflect exposure of 1976 patients to empagliflozin with a mean exposure duration of approximately 23 weeks. Patients received placebo (n=995), empagliflozin 10 mg (n=999), or empagliflozin 25 mg (n=977) once daily. The mean age of the population was 56 years and 3% were older than 75 years of age. More than half (55%) of the population was male; 46% were white, 50% were Asian, and 3% were Black or African American. At baseline, 57% of the population had diabetes more than 5 years and had a mean hemoglobin A1c (HbA1c) of 8%. Established microvascular complications of diabetes at baseline included diabetic nephropathy (7%), retinopathy (8%), or neuropathy (16%). Baseline renal function was normal or mildly impaired in 91% of patients and moderately impaired in 9% of patients (mean eGFR 86.8 mL/min/1.73 m^2).
Table 2 shows common adverse reactions (excluding hypoglycemia) associated with the use of empagliflozin. The adverse reactions were not present at baseline, occurred more commonly on empagliflozin than on placebo and occurred in greater than or equal to 2% of patients treated with empagliflozin 10 mg or empagliflozin 25 mg.

Adverse Reactions	**Placebo (%) N=995**	**Empagliflozin 10 mg (%) N=999**	**Empagliflozin 25 mg (%) N=977**

Urinary tract infection[a]	7.6	9.3	7.6
Female genital mycotic infections[b]	1.5	5.4	6.4
Upper respiratory tract infection	3.8	3.1	4.0
Increased urination[c]	1.0	3.4	3.2
Dyslipidemia	3.4	3.9	2.9
Arthralgia	2.2	2.4	2.3
Male genital mycotic infections[d]	0.4	3.1	1.6
Nausea	1.4	2.3	1.1
[a]Predefined adverse event grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis			

Adverse Reactions	**Placebo (%) N=995**	**Empagliflozin 10 mg (%) N=999**	**Empagliflozin 25 mg (%) N=977**
[b]Female genital mycotic infections include the following adverse reactions: vulvovaginal mycotic infection, vaginal infection, vulvitis, vulvovaginal candidiasis, genital infection, genital candidiasis, genital infection fungal, genitourinary tract infection, vulvovaginitis, cervicitis, urogenital infection fungal, vaginitis bacterial. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=481), empagliflozin 10 mg (N=443), empagliflozin 25 mg (N=420). [c]Predefined adverse event grouping, including, but not limited to, polyuria, pollakiuria, and nocturia [d]Male genital mycotic infections include the following adverse reactions: balanoposthitis, balanitis, genital infections fungal, genitourinary tract infection, balanitis candida, scrotal abscess, penile infection. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=514), empagliflozin 10 mg (N=556), empagliflozin 25 mg (N=557).			

Table 2 Adverse Reactions Reported in ≥2% of Patients Treated with Empagliflozin and Greater than Placebo in Pooled Placebo-Controlled Clinical Studies of Empagliflozin Monotherapy or Combination Therapy

Thirst (including polydipsia) was reported in 0%, 1.7%, and 1.5% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Volume Depletion

Empagliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. In the pool of five placebo-controlled clinical trials, adverse reactions related to volume depletion (e.g., blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolemia, orthostatic hypotension, and syncope) were reported by 0.3%, 0.5%, and 0.3% of patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Empagliflozin may increase the risk of hypotension in

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patients at risk for volume contraction. Increased Urination
In the pool of five placebo-controlled clinical trials, adverse reactions of increased urination (e.g., polyuria, pollakiuria, and nocturia) occurred more frequently on empagliflozin than on placebo (see TABLE 2). Specifically, nocturia was reported by 0.4%, 0.3%, and 0.8% of patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.
Hypoglycemia
The incidence of hypoglycemia by study is shown in Table 3. The incidence of hypoglycemia increased when empagliflozin was administered with insulin or sulfonylurea.

[a]Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL
[b]Severe hypoglycemic events: requiring assistance regardless of blood glucose [c]Treated set (patients who had received at least one dose of study drug) [d]Insulin dose could not be adjusted during the initial 18 week treatment period

Monotherapy (24 weeks)	**Placebo (n=229)**	**Empagliflozin 10 mg (n=224)**	**Empagliflozin 25 mg (n=223)**
Overall (%)	0.4	0.4	0.4
Severe (%)	0	0	0
In Combination with Metformin (24 weeks)	**Placebo + Metformin (n=206)**	**Empagliflozin 10 mg + Metformin (n=217)**	**Empagliflozin 25 mg + Metformin (n=214)**
Overall (%)	0.5	1.8	1.4
Severe (%)	0	0	0
In Combination with Metformin + Sulfonylurea (24 weeks)	**Placebo (n=225)**	**Empagliflozin 10 mg + Metformin + Sulfonylurea (n=224)**	**Empagliflozin 25 mg + Metformin + Sulfonylurea (n=217)**
Overall (%)	8.4	16.1	11.5
Severe (%)	0	0	0
In Combination with Pioglitazone +/- Metformin (24 weeks)	**Placebo (n=165)**	**Empagliflozin 10 mg + Pioglitazone +/- Metformin (n=165)**	**Empagliflozin 25 mg + Pioglitazone +/- Metformin (n=168)**
Overall (%)	1.8	1.2	2.4

Severe (%)	0	0	0
In Combination with Basal Insulin +/- Metformin (18 weeks[d])	**Placebo (n=170)**	**Empagliflozin 10 mg (n=169)**	**Empagliflozin 25 mg (n=155)**
Overall (%)	20.6	19.5	28.4
Severe (%)	0	0	1.3
In Combination with MDI Insulin +/- Metformin (18 weeks[d])	**Placebo (n=188)**	**Empagliflozin 10 mg (n=186)**	**Empagliflozin 25 mg (n=189)**
Overall (%)	37.2	39.8	41.3
Severe (%)	0.5	0.5	0.5

Table 3 Incidence of Overall[a] and Severe[b] Hypoglycemic Events in Placebo-Controlled Clinical Studies[c]

Genital Mycotic Infections

In the pool of five placebo-controlled clinical trials, the incidence of genital mycotic infections (e.g., vaginal mycotic infection, vaginal infection, genital infection fungal, vulvovaginal candidiasis, and vulvitis) was increased in patients treated with empagliflozin compared to placebo, occurring in 0.9%, 4.1%, and 3.7% of patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with either empagliflozin 10 or 25 mg.

Genital mycotic infections occurred more frequently in female than male patients (see TABLE 2). Phimosis occurred more frequently in male patients treated with empagliflozin 10 mg (less than 0.1%) and empagliflozin 25 mg (0.1%) than placebo (0%).

Urinary Tract Infections

In the pool of five placebo-controlled clinical trials, the incidence of urinary tract infections (e.g., urinary tract infection, asymptomatic bacteriuria, and cystitis) was increased in patients treated with empagliflozin compared to placebo (see TABLE 2). Patients with a history of chronic or recurrent urinary tract infections were more likely to experience a urinary tract infection. The rate of treatment discontinuation due to urinary tract infections was 0.1%, 0.2%, and 0.1% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Urinary tract infections occurred more frequently in female patients. The incidence of urinary tract infections in female patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg was 16.6%, 18.4%, and 17.0%, respectively. The incidence of urinary tract infections in male patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg was 3.2%, 3.6%, and 4.1%, respectively.

Metformin

The most common (>5%) established adverse reactions due to initiation of metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

In a 24-week clinical trial in which extended-release metformin or placebo was added to

glyburide therapy, the most common (>5% and greater than placebo) adverse reactions in the combined treatment group were hypoglycemia (13.7% vs 4.9%), diarrhea (12.5% vs 5.6%), and nausea (6.7% vs 4.2%).

Laboratory Tests

Empagliflozin

Increases in Serum Creatinine and Decreases in eGFR: Initiation of empagliflozin causes an increase in serum creatinine and decrease in eGFR within weeks of starting therapy and then these changes stabilize. In a study of patients with moderate renal impairment, larger mean changes were observed. In a long-term cardiovascular outcomes trial, the increase in serum creatinine and decrease in eGFR generally did not exceed 0.1 mg/dL and -9.0 mL/min/1.73 m^2, respectively, at Week 4, and reversed after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with empagliflozin.

Increase in Low-Density Lipoprotein Cholesterol (LDL-C): Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in patients treated with empagliflozin. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups.

Increase in Hematocrit: In a pool of four placebo-controlled studies, median hematocrit decreased by 1.3% in placebo and increased by 2.8% in empagliflozin 10 mg and 2.8% in empagliflozin 25 mg-treated patients. At the end of treatment, 0.6%, 2.7%, and 3.5% of patients with hematocrits initially within the reference range had values above the upper limit of the reference range with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Metformin

Decrease in Vitamin B12: In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of patients.

Postmarketing Experience

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

Empagliflozin

Gastrointestinal Disorders: Constipation

Infections: Necrotizing fasciitis of the perineum (Fournier's gangrene), urosepsis and pyelonephritis

Metabolism and Nutrition Disorders: Ketoacidosis

Renal and Urinary Disorders: Acute kidney injury

Skin and Subcutaneous Tissue Disorders: Angioedema, skin reactions (e.g., rash, urticaria)

Metformin hydrochloride

Hepatobiliary Disorders: Cholestatic, hepatocellular, and mixed hepatocellular liver injury

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

In the event of an overdose with Empagliflozin and Metformin Extended-Release Tablets, contact the Poison Control Center. Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of empagliflozin by hemodialysis has not been studied. However, metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful partly for removal of accumulated metformin from patients in whom Empagliflozin and Metformin Extended-Release Tablets overdosage is suspected.

Metformin hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

Glifempa xr contains: empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and metformin, a biguanide.

Mechanism of action

*Empagliflozin*Sodium-glucose co-transporter 2 (SGLT2) is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion. Empagliflozin is a reversible, highly potent (IC_{50} 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

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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 HCl

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. It is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike SUs, metformin does not produce hypoglycemia in either patients with type 2 diabetes mellitus or normal subjects (except in special circumstances) and does not cause hyperinsuliemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Empagliflozin

Urinary Glucose Excretion

In patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg empagliflozin once daily. Data

from single oral doses of empagliflozin in healthy subjects indicate that, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg and 25 mg doses.

Urinary Volume

In a 5-day study, mean 24-hour urine volume increase from baseline was 341 mL on Day 1 and 135 mL on Day 5 of empagliflozin 25 mg once daily treatment.

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, crossover study, 30 healthy subjects were administered a single oral dose of empagliflozin 25 mg, empagliflozin 200 mg (8 times the maximum dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

5.2 **Pharmacokinetic properties**

GLIFEMPA XR

Administration of *GLIFEMPA XR* with food resulted in no change in overall exposure of empagliflozin. For metformin hydrochloride extended-release high-fat meals increased systemic exposure to metformin (as measured by area-under-the-curve [AUC]) by

approximately 70% relative to fasting, while Cmax is not affected. Meals prolonged Tmax by approximately 3 hours.

Empagliflozin

Absorption The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes and no clinically relevant differences were noted between the two populations. After oral administration, peak plasma concentrations of empagliflozin were reached at 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, respectively, with 10 mg empagliflozin once daily treatment, and 4740 nmol·h/L and 687 nmol/L, respectively, with 25 mg empagliflozin once daily treatment. Systemic exposure of empagliflozin increased in a dose-proportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar, suggesting linear pharmacokinetics with respect to time.

Distribution The apparent steady-state volume of distribution was estimated to be 73.8 L based on a population pharmacokinetic analysis. Following administration of an oral ^{14}C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

Metabolism No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite was less than 10% of total drug-related material. *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 The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. Following once- daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state, which was consistent with empagliflozin half-life. Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%). The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

Metformin hydrochloride

Absorption Following a single oral dose of 1000 mg (2 x 500 mg tablets) metformin hydrochloride extended- release after a meal, the time to reach maximum plasma metformin concentration (Tmax) is achieved at approximately 7 to 8 hours. In both single-and multiple-dose studies in healthy subjects, once daily 1000 mg (2 x 500 mg tablets) dosing provides equivalent systemic exposure, as measured by AUC, and up to 35% higher Cmax of metformin relative to the immediate-release given as 500 mg twice daily.

Single oral doses of metformin hydrochloride extended-release from 500 mg to 2500 mg resulted in less than proportional increase in both AUC and Cmax. Low-fat and high-fat meals increased the systemic exposure (as measured by AUC) from metformin extended-release tablets by about 38% and 73%, respectively, relative to fasting. Both meals prolonged metformin Tmax by approximately 3 hours but Cmax was not affected.

Distribution The apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin hydrochloride tablets 850 mg averaged

654±358 L. Metformin is negligibly bound to plasma proteins, in contrast to SUs, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride tablets, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 mcg/mL. During controlled clinical trials of metformin hydrochloride, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

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

Specific Populations

Renal Impairment

Empagliflozin and metformin extended-release tablets:

Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of empagliflozin and metformin extended-release tablets in renally impaired patients have not been performed.

Empagliflozin: In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m^2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m^2), and severe (eGFR: less than 30 mL/min/1.73 m^2) renal impairment and subjects with kidney failure/end stage renal disease (ESRD) patients, 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. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR.

Metformin hydrochloride: In patients with decreased renal function (based on measured eGFR), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in eGFR.

Hepatic Impairment

Empagliflozin and metformin extended-release tablets:

Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of empagliflozin and metformin extended-release tablets in hepatically impaired patients have not been performed.

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

Metformin hydrochloride: No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

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Effects of Age, Body Mass Index, Gender, and Race

Empagliflozin: Based on the population PK analysis, age, body mass index (BMI), gender and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of empagliflozin.

Metformin hydrochloride: Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes mellitus, the antihyperglycemic effect of metformin was comparable in males and females.

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin hydrochloride in patients with type 2 diabetes mellitus, the antihyperglycemic effect was comparable in Caucasians (n=249), Blacks (n=51), and Hispanics (n=24).

Geriatric

Empagliflozin and metformin extended-release tablets:

Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of empagliflozin and metformin extended-release tablets in geriatric patients have not been performed.

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

Metformin hydrochloride: Limited data from controlled pharmacokinetic studies of metformin hydrochloride in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and Cmax is increased, compared with healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatric

Studies characterizing the pharmacokinetics of empagliflozin or metformin after administration of empagliflozin and metformin extended-release tablets in pediatric patients have not been performed.

5.3 **Preclinical safety data**

Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been conducted with the combination of empagliflozin and metformin hydrochloride to evaluate carcinogenesis, mutagenesis, or impairment of fertility. General toxicity studies in rats up to 13 weeks were performed with the combined components. These studies indicated that no additive toxicity is caused by the combination of empagliflozin and metformin.

Empagliflozin

Carcinogenesis Carcinogenesis was evaluated in 2-year studies conducted in CD-1 mice and Wistar rats. Empagliflozin did not increase the incidence of tumors in female rats dosed at 100, 300, or 700 mg/kg/day (up to 72 times the exposure from the maximum clinical dose of 25 mg). In male rats, hemangiomas of the mesenteric lymph node were increased significantly at 700 mg/kg/day or approximately 42 times the exposure from a 25 mg clinical dose. Empagliflozin did not increase the incidence of tumors in female mice dosed at 100, 300, or 1000 mg/kg/day (up to 62 times the exposure from a 25 mg clinical dose). Renal tubule adenomas and carcinomas were observed in male mice at 1000 mg/kg/day, which is approximately 45 times the exposure of the maximum clinical dose of 25 mg. These tumors may be associated with a metabolic pathway predominantly present in the male mouse kidney.

Mutagenesis Empagliflozin was not mutagenic or clastogenic with or without metabolic activation in the *in*

vitro Ames bacterial mutagenicity assay, the *in vitro* L5178Y tk mouse lymphoma cell assay, and an *in vivo*
micronucleus assay in rats.

Impairment of Fertility

Empagliflozin had no effects on mating, fertility or early embryonic development in treated male or female rats up to the high dose of 700 mg/kg/day (approximately 155 times the 25 mg clinical dose in males and females, respectively).

Metformin hydrochloride

Carcinogenesis Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2000 mg/kg/day based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

Mutagenesis There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*Salmonella typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Impairment of Fertility Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 2 times the MRHD based on body surface area comparisons.

6. Pharmaceutical particulars

6.1 List of excipients

Carbomer (as Acrypol-912G) Carbomer (as Acrypol-934P)
Hydroxy Propyl Methyl Cellulose-K100M Hydroxy Propyl Methyl Cellulose-K4M Hydroxy Propyl Methyl Cellulose-K15M
Methacrylic Acid & Methyl Methacrylate Copolymer 1:2 (as Acrycoat S-100) Purified Talc
Magnesium Stearate
Colour Titanium Dioxide Isopropyl Alcohol Povidone (As PVPK-30)
Microcrystalline Cellulose Mannitol
Crospovidone
Colour Tartrazine FCF Purified Water

6.2 Incompatibilities

Not applicable

N

6.3 Shelf life

36 months

6.4 Special precautions for storage

Stored at a temperature not exceeding 30°C, in a cool and dark place, protect from direct sunlight.

6.5 Nature and contents of container

3 x 10 pack: 10 tablets packed in alu-alu blister and such 3 blisters are packed in single carton along with pack insert.

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.

7. Marketing authorisation holder

GALAXY PHARMACEUTICAL LTD.
1st Floor, Doctors Park, 3rd Parkland Avenue, P.O.BOX 39107 - 00623,
Nairobi (Kenya).

8. Marketing Authorization Number

CTD10089

9. Date of first authorization/renewal of the authorization

06/10/2023

10. Date of revision of the text

10/05/2025