SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. **Name of the medicinal product**

   GLIFEMPA M 25/500 (EMPAGLIFLOZIN 25 MG AND METFORMIN HCL 500 MG TABLETS)

2. **Qualitative and quantitative composition**

   GLIFEMPA M 25/500 (EMPAGLIFLOZIN 25 MG AND METFORMIN HCL 500 MG TABLETS)

   Each film coated tablet contains:

   - Empagliflozin (In House) (25 mg)
   - Metformin Hydrochloride BP (500 mg)
   - Approved colour used (-)
   - -- (-- QS)

   Batch Size : 16,000 Tablets

Sr. No.	Ingredients	Specification	Qty. mg/ Tablet	Qty. Kg/ batch	Overages (%)
1.	Metformin Hydrochloride	BP	500.00	8.00	---
2.	PEG- 4000	BP	40.00	0.640	---
3.	P.V.P. K-30	BP	10.00	0.160	---
4.	Empagliflozin	In House	25.00	0.400	
5.	Silicified Microcrystalline cellulose pH 102	NF	19.25	0.308	
6.	Mannitol	BP	20.00	0.320	---
7.	Talcum	BP	4.00	0.064	---
8.	Sodium starch Glycolate	BP	5.75	0.092	---
9.	Aerosil	BP	2.00	0.032	
10.	Magnesium stearate	BP	5.00	0.080	
11.	Purified Water	IH	q.s		
	Total		**631.00**		
	FILM COATING				
12.	Hypromellose	BP	15.00	0.240	---

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

	(HPMC E -15)				
13.	Polyethylene glycol	BP	1.20	0.019	---
14.	Iron oxide yellow	In-house	2.00	0.032	---
15.	PEG 6000	BP	1.20	0.019	
16.	Purified Talc	BP	3.60	0.058	
17.	*Iso Propyl Alcohol	BP	120.40	1.926	---
18.	*Methylene Dichloride	BP	240.80	3.853	---
	Total		**654.00**		

* Isopropyl Alcohol and Methylene Dichloride are used as solvent and not found in the final product.

Weight of compressed tablet : 631.00 mg ± 5 %

Weight of coated tablet : 654.00 mg ± 5 %

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

3. Pharmaceutical form

Film-coated Tablets

GLIFEMPA M 25/500 (EMPAGLIFLOZIN 25 MG AND METFORMIN HCL 500 MG TABLETS)

Description: Yellow coloured, capsule shaped, biconvex, film coated tablet, plain on both sides.

4. Clinical particulars

4.1 Therapeutic indications

Glifempa 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

Route of administration: Oral

Posology

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

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

Renal impairment

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

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, Glifempa M should be used with caution in these patients.

Paediatric population

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

Method of administration

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

4.3 Contraindications

• Hypersensitivity to the active substances or to any of the excipients.

• Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)

• Diabetic pre-coma.

• Severe renal failure (GFR <30 ml/min).

• 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

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.

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.

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 function

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

Cardiac function

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

function. For patients with acute and unstable heart failure, Glifempa M is contraindicated due to the metformin component.

Hepatic injury

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

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 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.

Urinary tract infections

In the pooled placebo-controlled double-blind trials of 18 to 24 weeks duration, the overall frequency of urinary tract infection reported as adverse event was higher in patients treated with empagliflozin 10 mg on a background of metformin compared to patients treated with placebo or empagliflozin 25 mg on a background of metformin. Post-marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin.

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot care.

Elderly

The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the hydration status. Patients aged 75 years and older may be at an increased risk of

volume depletion. Therefore, special attention should be given to their volume intake in case of co-administered medicinal products which may lead to volume depletion (e.g. diuretics, ACE inhibitors). Therapeutic experience in patients aged 85 years and older is limited. Initiation of therapy in this population is not recommended

Cardiac failure

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

Urine laboratory assessments

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

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

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.

Empagliflozin

Pharmacodynamic interactions

Diuretics

As Glifempa M contains empagliflozin it 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 (C_{max}) 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 on empagliflozin has not been studied. Co-medication with known inducers of UGT enzymes should be avoided due to a potential risk of decreased efficacy.

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

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

Effects of empagliflozin on other medicinal products

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

Empagliflozin does not inhibit P-gp at therapeutic doses. Based on in vitro studies, empagliflozin is considered unlikely to cause interactions with medicinal products 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 C_{max} of digoxin. These changes were not considered to be clinically meaningful.

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

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

Metformin

Concomitant use not recommended

Alcohol

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

Organic cation transporters (OCT)

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

• Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.

• Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.

• Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.

• Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

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.

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.

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.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

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

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

4.7 Effects on ability to drive and use machines

Not available

4.8 Undesirable effects

Summary of the safety profile

A total of 12245 patients with type 2 diabetes were treated in clinical studies to evaluate the safety of empagliflozin as add-on to metformin, of which 8199 patients were treated with empagliflozin as add-on to metformin either alone or in addition to a sulfonylurea, pioglitazone, or insulin.

Placebo controlled double-blinded trials of 18 to 24 weeks of exposure included 3456 patients, of which 1271 were treated with empagliflozin 10 mg as add-on to metformin and 1259 with empagliflozin 25 mg as add-on to metformin. The most commonly reported adverse events in clinical trials were hypoglycaemia in combination with insulin and/or sulphonylurea, urinary tract infections, genital tract infections and increased urination. 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.

Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.

Description of selected adverse reactions

Hypoglycaemia

The frequency of hypoglycaemia depended on the background therapy in the respective studies and was similar for empagliflozin and placebo as add-on to metformin, as add-on to linagliptin and metformin, for the combination of empagliflozin with metformin in drug-naïve patients compared to those treated with empagliflozin and metformin as individual components, and as adjunct to standard care therapy.

Major hypoglycaemia (events requiring assistance)

The overall frequency of patients with major hypoglycaemic events was low (<1%) and similar for empagliflozin and placebo as add-on to metformin, and for the combination of empagliflozin with metformin in drug-naïve patients compared to those treated with empagliflozin and metformin as individual components, and as adjunct to standard care therapy. Major hypoglycaemic events occurred in 0.5%, 0% and 0.5% of patients treated with empagliflozin 10 mg, empagliflozin 25 mg and placebo when added on to metformin and insulin, respectively.

Urinary tract infection

The overall frequency of urinary tract infection adverse events was higher in metformin-treated patients who received empagliflozin 10 mg (8.8%) compared to empagliflozin 25 mg (6.6%) or placebo (7.8%). Similar to placebo, urinary tract infection was reported more frequently for empagliflozin in patients with a history of chronic or recurrent urinary tract infections.

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently in metformin-treated patients who received empagliflozin 10 mg (4.0%) and empagliflozin 25 mg (3.9%) compared to placebo (1.3%) and were reported more frequently for empagliflozin compared to placebo in female patients.

Increased urination

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

Volume depletion

The overall frequency of volume depletion (including the predefined terms blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolaemia, orthostatic hypotension, and syncope) in metformin-treated patients who received empagliflozin was low: 0.6% for empagliflozin 10 mg, 0.3% for empagliflozin 25 mg and 0.1% for placebo.

Blood creatinine increased/Glomerular filtration rate decreased

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

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.

Treatment of over dosage:

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.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

Mechanism of Action:

Glifempa 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 (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.

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.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

5.2 Pharmacokinetic properties

The results of a bioequivalence study in healthy subjects demonstrated that GLIFEMPA M 10/500 (empagliflozin/metformin hydrochloride) 5 mg/500 mg, 5 mg/1000 mg, 12.5 mg/500 mg, and 12.5 mg/1000 mg combination tablets are bioequivalent to coadministration of corresponding doses of empagliflozin and metformin as individual tablets.

Administration of 12.5 mg empagliflozin/1000 mg metformin under fed conditions resulted in a 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.

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 doseproportional 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. Administration of 25 mg empagliflozin after intake of a high-fat and high-calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and Cmax decreased 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. 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 [14C]-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 [14C]-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 The absolute bioavailability of a metformin hydrochloride 500-mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin tablets 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower Cmax, a 25% lower AUC, and a 35 minute prolongation of time to peak plasma concentration (Tmax) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

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 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, 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.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

No animal studies have been conducted with the combination of empagliflozin and metformin 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.

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

Sr. No.	Ingredients	Specification
1.	PEG- 4000	BP
2.	P.V.P. K-30	BP
3.	Silicified Microcrystalline cellulose pH 102	NF
4.	Mannitol	BP
5.	Talcum	BP
6.	Sodium starch Glycolate	BP
7.	Aerosil	BP
8.	Magnesium stearate	BP
9.	Purified Water	IH
10.	Hypromellose (HPMC E -15)	BP
11.	Propylene glycol	BP
12.	Iron oxide yellow	In-house
13.	PEG 6000	BP

14.	Purified Talc	BP
15.	*Iso Propyl Alcohol	BP
16.	*Methylene Dichloride	BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C.

Protect from direct sunlight, heat and moisture.

Keep all medicines out of reach of children.

6.5 Nature and contents of container

Blister pack of 10 tablets

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

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8. Marketing authorisation number(s)

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9. Date of first authorisation/renewal of the authorisation

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10. Date of revision of the text

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Application Number	
Date of submission of the dossier	

1.18 Batch number(s) of the FPPs used in

Clinical/ Bioequivalence studies	Not Applicable		
Stability studies	FTT024	FTT025	FTT026
Validation/ Production scale batches	FT 767	FT 768	FT 769

Batch size: 50,000 Tablets

Composition of clinical, primary stability and validation/ production FPP batches (kg)

Ingredients	Administration Unit		Bioequivalence <batch number>		Primary stability <batch number>		Production <batch number>	
	Mg	%*	Kg	%*	Kg	%*	kg	%*
Metformin Hydrochloride	500.00	8.00	--	--	--	--	--	--
PEG- 4000	40.00	0.640	--	--	--	--	--	--
P.V.P. K-30	10.00	0.160	--	--	--	--	--	--
Empagliflozin	25.00	0.400	--	--	--	--	--	--
Silicified Microcrystalline cellulose pH 102	19.25	0.308	--	--	--	--	--	--
Mannitol	20.00	0.320	--	--	--	--	--	--
Talcum	4.00	0.064	--	--	--	--	--	--
Sodium starch Glycolate	5.75	0.092	--	--	--	--	--	--
Aerosil	2.00	0.032	--	--	--	--	--	--
Magnesium stearate	5.00	0.080						
Purified Water	q.s							
Total	**631.00**							
FILM COATING								
Hypromellose (HPMC E -15)	15.00	0.240	--	--	--	--	--	--
Propylene Glycol	1.20	0.019	--	--	--	--	--	--
Iron Oxide Yellow	2.00	0.032	--	--	--	--	--	--
PEG 6000	1.20	0.019	--	--	--	--	--	--
Purified Talc	3.60	0.058	--	--	--	--	--	--

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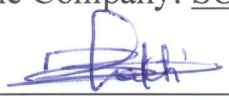
Iso Propyl Alcohol	120.40	1.926	--	--	--	--	--	--
Methylene Dichloride	240.80	3.853	--	--	--	--	--	--
Total	**654.00**							
Equivalence of the composition or justified differences 654.00 mg ≡ 100%								
* Each ingredient is expressed as a percentage of the grand total.								
For PPB use only								

DECLARATION BY AN APPLICANT

1. I, the undersigned certify that all the information in this application form and accompanying documentation is correct, complete and true to the best of my knowledge.
2. I further confirm that the information referred to in my application dossier is available for verification during current GMP inspection.
3. I agree that the undersigned has not marketed or advertised this product in Kenya and will follow the PPB requirements for advertisements of medicines
4. I also agree that the undersigned will implement a Pharmacovigilance plans for this product in accordance with PPB requirements
5. I also agree that I am obliged to follow the requirements of the Pharmacy and Poisons Act, which are related to pharmaceutical products.
6. I also consent to the processing of information provided by the Pharmacy and Poisons Board.

Name: DR. BHAKTI DEVJI CHHABHAIYA

Position in the Company: SUPERINTENDENT PHARMACIST

Signature: 

Official stamp:

GALAXY PHARMACEUTICAL LTD.
P.O. Box 39107-00623
NAIROBI, KENYA
Tel: 3748551/2/3/4