SUMMARY OF PRODUCT CHARACTERISTICS

1.	**Name of the Medical Product**
	1.1 Product Name : EMPADIL M 12.5/500 (Empagliflozin 12.5 mg and Metformin Hydrochloride 500 mg Tablets) **EMPADIL M 12.5/1000 (Empagliflozin 12.5 mg and Metformin Hydrochloride 1000 mg Tablets)**
	1.2 Strength : **EMPADIL M 12.5/500 (Empagliflozin 12.5 mg and Metformin Hydrochloride 500 mg Tablets)** **Each film coated tablet contains:** Empagliflozin IH…….12.5 mg Metformin Hydrochloride USP…….500 mg Excipients…….q.s. Colour : Titanium Dioxide, Yellow Iron Oxide, Red Iron Oxide **EMPADIL M 12.5/1000 (Empagliflozin 12.5 mg and Metformin Hydrochloride 1000 mg Tablets)** **Each film coated tablet contains:** Empagliflozin IH…….12.5 mg Metformin Hydrochloride USP…….1000 mg Excipients…….q.s. Colour : Titanium Dioxide, Yellow Iron Oxide, Red Iron Oxide
	1.3 Pharmaceutical Dosage Form : Film Coated Tablets
2.	**Qualitative & Quantitative Composition:** **EMPADIL M 12.5/500 (Empagliflozin 12.5 mg and Metformin Hydrochloride 500 mg Tablets)** **Each film coated tablet contains:** Empagliflozin IH…….12.5 mg Metformin Hydrochloride USP…….500 mg Excipients…….q.s. Colour : Titanium Dioxide, Yellow Iron Oxide, Red Iron Oxide **EMPADIL M 12.5/1000 (Empagliflozin 12.5 mg and Metformin Hydrochloride 1000 mg Tablets)** **Each film coated tablet contains:** Empagliflozin IH…….12.5 mg Metformin Hydrochloride USP…….1000 mg Excipients…….q.s. Colour : Titanium Dioxide, Yellow Iron Oxide, Red Iron Oxide For a full list of excipients, see section 6.1 of SmPC
3.	**Pharmaceutical Form:** Film Coated Tablets
	Film Coated Tablets **EMPADIL M 12.5/500 (Empagliflozin 12.5 mg and Metformin Hydrochloride 500 mg Tablets)** Pink coloured, oval shaped, biconvex, film-coated tablets, debossed “EM” on one side and “2” on other side **EMPADIL M 12.5/1000 (Empagliflozin 12.5 mg and Metformin Hydrochloride 1000 mg Tablets)** Pink coloured, oval shaped, biconvex, film-coated tablets, debossed “EM” on one side and “4” on other side
4.	**Clinical Particulars**

4.1 Therapeutic Indications:

Empagliflozin and metformin combination is 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
Empagliflozin and Metformin 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:

Prior to Initiation of Empagliflozin and Metformin
Assess renal function before initiating Empagliflozin and Metformin and as clinically indicated In patients with volume depletion, correct this condition before initiating Empagliflozin and Metformin.
Recommended Dosage and Administration

- Individualize the starting dose of Empagliflozin and Metformin based on the patient's current regimen:
  - In patients on metformin, switch to empagliflozin and metformin containing empagliflozin 5 mg with a similar total daily dose of metformin;
  - In patients on empagliflozin, switch to empagliflozin and metformin containing metformin 500 mg with a similar total daily dose of empagliflozin;
  - In patients already treated with empagliflozin and metformin, switch to Empagliflozin and Metformin containing the same total daily doses of each component.
- Monitor effectiveness and tolerability, and adjust dosing as appropriate, not to exceed the maximum recommended daily dose of empagliflozin 25 mg and metformin 2000 mg.
- Take empagliflozin and metformin twice daily with meals; with gradual dose escalation to reduce the gastrointestinal side effects due to metformin.

Pediatric Use

- Safety and effectiveness of Empagliflozin and Metformin have not been established in pediatric patients.

Geriatric Use

- Because renal function abnormalities can occur after initiating empagliflozin, metformin is substantially excreted by the kidney, and aging can be associated with reduced renal function, renal function should be assessed more frequently in elderly patients.

Dosage Recommendations in Patients with Renal Impairment

- Initiation of Empagliflozin and Metformin is not recommended in patients with an eGFR less than 45 mL/min/1.73 m^2, due to the metformin component.
- Empagliflozin and Metformin is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 or in patients on dialysis.

Hepatic Impairment

	Use of metformin hydrochloride in patients with hepatic impairment has been associated with some cases of lactic acidosis. Empagliflozin and Metformin is not recommended in patients with hepatic impairment. ***Discontinuation for Iodinated Contrast Imaging Procedures*** Discontinue Empagliflozin and Metformin 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 empagliflozin and metformin if renal function is stable
	4.3 Contraindications: Empagliflozin and Metformin 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 empagliflozin and metformin, reactions such as angioedema have occurred.
	4.4 Special warning and precautions for use: <u>*Lactic Acidosis*</u> There have been post marketing 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 empagliflozin and metformin. In empagliflozin and metformin -treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin is dialyzable, with a clearance of up to 170 mL/minute under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery. Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur, instruct them to discontinue Empagliflozin and Metformin 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 empagliflozin and metformin, obtain an estimated glomerular filtration rate (eGFR).
- Empagliflozin and Metformin 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 Empagliflozin and Metformin. 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 empagliflozin and metformin 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 empagliflozin and metformin 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 Empagliflozin and Metformin 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. Empagliflozin and Metformin 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 empagliflozin and metformin.

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 empagliflozin and metformin.

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 empagliflozin and metformin 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. Empagliflozin and Metformin is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with empagliflozin and metformin 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 may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, empagliflozin and metformin 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, 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 for at least 3 days prior to surgery.

Consider monitoring for ketoacidosis and temporarily discontinuing empagliflozin and metformin 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.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue empagliflozin and metformin 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 postmarketing 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 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. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.

Urosepsis and Pyelonephritis

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

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
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.

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 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, 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; treat promptly per standard of care, and monitor until signs and symptoms resolve. Empagliflozin and Metformin is contraindicated in patients with hypersensitivity to empagliflozin or any of the excipients in Empagliflozin and Metformin.

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 and manage any abnormalities.

4.5 Interactions with other medicinal products and other forms of Interactions :

Table 1. Clinically Relevant Interactions with Empagliflozin and Metformin	
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 Empagliflozin and Metformin 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 Empagliflozin and Metformin.
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 Empagliflozin and Metformin, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating Empagliflozin and Metformin. 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	Co- administration of Empagliflozin and Metformin 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.

Intervention	When such drugs are administered to a patient receiving Empagliflozin and Metformin, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving Empagliflozin and Metformin, 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.	

4.6 Pregnancy and Lactation:

Pregnancy

Based on animal data showing adverse renal effects from empagliflozin, Empagliflozin and Metformin is not recommended during the second and third trimesters of pregnancy.

The limited available data with Empagliflozin and Metformin combination 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 combination, 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.

Lactation

There is limited information regarding the presence of Empagliflozin and Metformin combination 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 combination is not recommended while breastfeeding.

Females and Males of Reproductive Potential

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

4.7 Effects on ability to drive and use machine:

Not applicable.

4.8 Undesirable Effects:
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.

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 2.

Table 2. 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

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

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.

Table 3. 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

[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, and 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).

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. Empagliflozin may increase the risk of hypotension in patients at risk for volume contraction.

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.

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.

	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. *Increase in Hematocrit:* Increased median hematocrit were observed in patients treated with empagliflozin 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.
	4.9 Overdosage: In the event of an overdose with Empagliflozin and Metformin. Overdose of metformin has occurred, including ingestion of amounts greater than 50 grams. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected. Removal of empagliflozin by hemodialysis has not been studied
5.	**Pharmacological properties**
	5.1 Pharmacodynamic Properties: **Pharmacotherapeutic group:** Sodium-glucose co-transporter 2 (SGLT2 inhibitor, antihyperglycemic agent **Empagliflozin :ATC Code:** A10BK03 **Metformin : ATC Code:** A10BA02 **Mechanism of Action** **Empagliflozin and Metformin combination** Empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and metformin, a biguanide. **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. **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 hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and daylong plasma insulin response may actually decrease.
	5.2 Pharmacokinetics Properties: **Empagliflozin and Metformin** Administration of 12.5 mg empagliflozin/1000 mg metformin hydrochloride 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 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. 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%. *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. *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.

Excretion: 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

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 hydrochloride 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. Metformin partitions into erythrocytes, most likely as a function of time.

Elimination

Metformin has 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.

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

Excretion: Following oral administration, approximately 90% of the absorbed drug is excreted via the renal route within the first 24 hours. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination

5.3 Preclinical Safety data:

Carcinogenesis, Mutagenesis, Impairment of Fertility

Empagliflozin and Metformin

No carcinogenicity, mutagenicity, or impairment of fertility studies have been conducted with the combination of empagliflozin and metformin HCl. 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 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. 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. 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** 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. 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. 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: **EMPADIL M 12.5/500 (Empagliflozin 12.5 mg and Metformin Hydrochloride 500 mg Tablets)** Crosspovidone, Hydroxypropyl Cellulose, Mannitol, Microcrystalline Cellulose, Colloidal Sillicon Dioxide, Magnesium Stearate and Purified Water, Opadry 03B84681 Pink IH **EMPADIL M 12.5/1000 (Empagliflozin 12.5 mg and Metformin Hydrochloride 1000 mg Tablets)** Crosspovidone, Hydroxypropyl Cellulose, Mannitol, Microcrystalline Cellulose, Colloidal Sillicon Dioxide, Magnesium Stearate and Purified Water, Opadry 03B84681 Pink IH
	6.2 Incompatibilities: Not applicable
	6.3 Shelf life: 24 months
	6.4 Special Precautions for storage: Store below 30ºC. protect from moisture.
	6.5 Nature and contents of container: 10 tablets in Alu-Alu Blister pack, 3 such blisters in a printed carton along with pack Insert.
	6.6 Special precautions for disposal: Not applicable
7.	**Marketing Authorization Holder:** Ajanta Pharma Limited Ajanta House, Charkop, Kandivli (West), Mumbai- 400 067, India **Manufacturing Site Address:**

	Z/103/A, Dahej SEZ II, Bharuch, Gujarat-392130, India Telephone : (0091) - 022- 66061000 Fax : (0091) - 022-66061200/300 e-mail : info@ajantapharma.com
8.	**Marketing Authorization Numbers:** Not applicable
9.	**Date of first registration /renewal of the registration:** Not Applicable
10.	**Date of revision of text: Apr 16, 2022**