FRONT

EMPADIL M

Empagliflozin and Metformin Hydrochloride Tablets

903214

COMPOSITION

EMPADIL M 5/500 (Empagliflozin and Metformin Hydrochloride Tablets 5/500 mg)
Each film coated tablet contains:

Empagliflozin IH	5 mg
Metformin Hydrochloride USP	500 mg
Excipients	q.s.

EMPADIL M 5/1000 (Empagliflozin and Metformin Hydrochloride Tablets 5/1000 mg)
Each film coated tablet contains:

Empagliflozin IH	5 mg
Metformin Hydrochloride USP	1000 mg
Excipients	q.s.

EMPADIL M 12.5/500 (Empagliflozin and Metformin Hydrochloride Tablets 12.5/500 mg)
Each film coated tablet contains:

Empagliflozin IH	12.5 mg
Metformin Hydrochloride USP	500 mg
Excipients	q.s.

EMPADIL M 12.5/1000 (Empagliflozin and Metformin Hydrochloride Tablets 12.5/1000 mg)
Each film coated tablet contains:

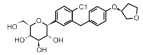
Empagliflozin IH	12.5 mg
Metformin Hydrochloride USP	1000 mg
Excipients	q.s.

DOSAGE FORM

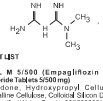
Film Coated Tablets
Category of Distribution : POM

DESCRIPTION

Empagliflozin:
D-Glucitol, 1,5-anhydro-1-C-[4-chloro-3-[[4-[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S), with molecular formula $C_{23}H_{27}ClO_7$; Empagliflozin having molecular weight of 450.91. The chemical structure is



Metformin Hydrochloride:
1, 1-dimethylbiguanide monohydrochloride with molecular formula $C_4H_{11}N_5.HCl$. Metformin having molecular weight of 165.63. The chemical structure is



EXCIPIENT LIST

EMPADIL M 5/500 (Empagliflozin and Metformin Hydrochloride Tablets 5/500 mg)
Crospovidone, Hydroxypropyl Cellulose, Mannitol, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Purified Water, Opadry 03B84681 Pink IH.

EMPADIL M 5/1000 (Empagliflozin and Metformin Hydrochloride Tablets 5/1000 mg)
Crospovidone, Hydroxypropyl Cellulose, Mannitol, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Purified Water, Opadry 03F52035 Yellow IH.

EMPADIL M 12.5/500 (Empagliflozin and Metformin Hydrochloride Tablets 12.5/500 mg)
Crospovidone, Hydroxypropyl Cellulose, Mannitol, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Purified Water, Opadry 03B84681 Pink IH.

EMPADIL M 12.5/1000 (Empagliflozin and Metformin Hydrochloride Tablets 12.5/1000 mg)
Crospovidone, Hydroxypropyl Cellulose, Mannitol, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Purified Water, Opadry 03B84681 Pink IH.

CLINICAL PARTICULARS

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.

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.

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.

Special warnings and precautions for use
Lactic Acidosis
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 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.
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.

Interaction with other medicinal products and other forms of interaction

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. Monitor serum bicarbonate levels to detect metabolic acidosis.
Intervention	Consider the 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.

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 7-times the maximum clinical dose caused renal pelvic and tubular 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.

Effects on ability to drive and use machines
Not applicable.

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 3408 patients with type 2 diabetes mellitus treated for 18 to 24 weeks, of which 926 patients received placebo, 1271 patients received a daily dose of empagliflozin 10 mg, and 1209 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 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	8.4	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 [1]	7.8	9.3	7.6
Female genital mycotic infections [2]	1.5	5.4	6.4
Upper respiratory tract infection [3]	3.8	3.1	4.0
Increased urination [4]	1.0	3.4	3.2
Dyslipidemia	3.4	3.9	2.9
Arthralgia	2.2	2.4	2.3
Male genital mycotic infections [5]	0.4	3.1	1.6
Nausea	1.4	2.3	1.1

[1] Predefined adverse event grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis
[2] 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).
[3] Predefined adverse event grouping, including, but not limited to, polyuria, pollakiuria, and nocturia
[4] 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: Decreased 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.

Overdose
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

Pharmacological properties
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 responses may actually decrease.

Pharmacokinetic properties
Empagliflozin and Metformin
Administration of 12.5 mg empagliflozin/1000 mg metformin

BACK

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, UGT1A9, 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 erythrocytic 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.

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

PHARMACEUTICAL PARTICULARS

Incompatibilities

Not applicable.

Shelf life

24 months

Storage Condition

Store below 30°C.

Name and Contents of Container

10 tablets in Al-Al Blister pack, 3 such blisters in a printed carton along with pack insert.

Ver: 00

Last Revision Date: May 02, 2022

Manufacturing Authorization Holder	Manufacturer
Ajanta Pharma Limited Ajanta House, Charkop Kandivli (West) Mumbai – 400067, India. Tel: 022-6913 2111/2112 Fax: 022-49132070 E m a i l : info@ajantapharma.com	Ajanta Pharma Limited, Factory - Z/103/A, Dahej SEZ II, Bharuch, Gujarat – 392130, India

EMPADIL M

Empagliflozin IH and Metformin Hydrochloride USP

PATIENT INFORMATION LEAFLET

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side, effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

Distribution Category: Prescription Only Medicine or POM

What is in this leaflet:

1. What Empagliflozin and Metformin is and what it is used for
2. Before you take Empagliflozin and Metformin
3. How to take Empagliflozin and Metformin
4. Possible side effects
5. How to store Empagliflozin and Metformin
6. Further information

1. What Empagliflozin and Metformin is and what it is used for

Empagliflozin and Metformin combination is a prescription medicine that contains 2 diabetes medicines, empagliflozin and metformin.

Empagliflozin and Metformin combination can be used:

- Along with diet and exercise to improve blood sugar in adults with type 2 diabetes.
- In adults with type 2 diabetes who have known cardiovascular disease when empagliflozin, one of the medicines in Empagliflozin and Metformin combination, is needed to reduce the risk of cardiovascular death.

Empagliflozin and Metformin combination is not for people with type 1 diabetes. It may increase their risk of diabetic ketoacidosis (increased ketones in blood or urine).

It is not known if Empagliflozin and Metformin combination is safe and effective in children.

2. What you need to know before you take Empagliflozin and Metformin

Do not take Empagliflozin and Metformin if you:

- have severe kidney problems, and stage renal disease or are on dialysis.
- have a condition called metabolic acidosis or diabetic ketoacidosis (increased ketones in the blood or urine).
- are allergic to empagliflozin, metformin, or any of the ingredients in Empagliflozin and Metformin combination. Symptoms of a serious allergic reaction to Empagliflozin and Metformin combination may include:
  - swelling of your face, lips, throat and other areas of your skin
  - difficulty with swallowing or breathing
  - raised, red areas on your skin (hives)

  If you have any of these symptoms, stop taking Empagliflozin and Metformin combination and call your healthcare provider right away or go to the nearest hospital emergency room.

Before taking Empagliflozin and Metformin combination, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems.
- have liver problems.
- have heart problems, including congestive heart failure.
- are 65 years of age or older.
- have a history of infection of the vagina or penis.
- have a history of urinary tract infection or problems with urination.
- are going to have surgery. Your healthcare provider may stop your Empagliflozin and Metformin combination before you have surgery. Talk to your healthcare provider if you are having surgery about when to stop taking Empagliflozin and Metformin combination and when to start it again.
- are eating less, or there is a change in your diet.
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas.
- drink alcohol very often or drink alot of alcohol in the short term ("binge" drinking).
- are going to get an injection of dye or contrast agents for an x-ray procedure. Empagliflozin and Metformin combination may need to be stopped for a short time. Talk to your healthcare provider about when you should stop Empagliflozin and Metformin combination and when you should start Empagliflozin and Metformin combination again.
- have type 1 diabetes. Empagliflozin and Metformin combination should not be used to treat people with type 1 diabetes.
- have low levels of vitamin B12 in your blood.
- are pregnant or plan to become pregnant. Empagliflozin and Metformin combination may harm your unborn baby. If you become pregnant while taking Empagliflozin and Metformin combination, tell your healthcare provider as soon as possible. Talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. Empagliflozin and Metformin combination may pass into your breast milk and may harm your baby. Talk with your healthcare provider about the best way to feed your baby if you are taking Empagliflozin and Metformin combination. Do not breastfeed while taking Empagliflozin and Metformin combination.
- are a person who has not gone through menopause (premenopausal) who does not have periods regularly or at all. Empagliflozin and Metformin combination can cause a rare release of an egg from an ovary in a person (ovulation). This can increase your chance of getting pregnant. Tell your healthcare provider right away if you become pregnant while taking Empagliflozin and Metformin combination.

Most important information I should know about Empagliflozin and Metformin combination

Empagliflozin and Metformin combination can cause serious side effects, including:

Lactic Acidosis. Metformin hydrochloride, one of the medicines in Empagliflozin and Metformin combination, can cause a rare but serious condition called lactic acidosis (a build-up of lactic acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in a hospital.

Stop taking Empagliflozin and Metformin combination and call your healthcare provider right away or go to the nearest hospital emergency room if you get any of the following symptoms of lactic acidosis:

- feel very weak and tired o have unusual sleepiness or sleep longer than usual
- have unusual (not normal) muscle pain o feel cold, especially in your arms and legs
- have trouble breathing o feel dizzy or lightheaded
- have unexplained stomach or intestinal problems with nausea and vomiting, or diarrhea
- have a slow or irregular heartbeat

You have a higher chance of getting lactic acidosis with Empagliflozin and Metformin combination if you:

- have moderate to severe kidney problems.
- have liver problems.
- drink a lot of alcohol (very often or short-term "binge" drinking).
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids.
- have certain x-ray tests with injectable dyes or contrast agents.
- have surgery or other procedure for which you need to restrict the amount of food and liquid you eat and drink.
- have congestive heart failure.
- have a heart attack, severe infection, or stroke.
- are 65 years of age or older.

Tell your healthcare provider if you have any of the problems in the list above. Tell your healthcare provider that you are taking Empagliflozin and Metformin combination before you have surgery or x-ray tests. Your healthcare provider may need to stop your Empagliflozin and Metformin combination for a while if you have surgery or certain x-ray tests. Empagliflozin and Metformin combination can have other serious side effects.

Ketoacidosis (increased ketones in your blood or urine). Ketoacidosis has happened in people who have type 1 diabetes or type 2 diabetes, during treatment with empagliflozin, one of the medicines in Empagliflozin and Metformin combination. Ketoacidosis has also happened in people with diabetes who were sick or who had surgery during treatment with Empagliflozin and Metformin combination.

Ketoacidosis is a serious condition, which needs to be treated in a hospital. Ketoacidosis may lead to death.

Ketoacidosis can happen with Empagliflozin and Metformin combination even if your blood sugar is less than 250 mg/dL.

Stop taking Empagliflozin and Metformin combination and call your healthcare provider right away or go to the nearest hospital emergency room if you get any of the following symptoms:

- nausea
- tiredness
- vomiting
- trouble breathing
- stomach-area (abdominal) pain

If you get any of these symptoms during treatment with Empagliflozin and Metformin combination, if possible, check for ketones in your urine, even if your blood sugar is less than 250 mg/dL.

Dehydration. Empagliflozin and Metformin combination can cause some people to become dehydrated (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension). There have been reports of sudden worsening of kidney function in people who are taking Empagliflozin and Metformin combination.

You may be at higher risk of dehydration if you:

- have kidney problems
- are on low sodium (salt) diet
- are 65 years of age or older
- take medicines to lower your blood pressure, including diuretics (water pills)

Talk to your healthcare provider about what you can do to prevent dehydration including how much fluid you should drink on a daily basis.

Talk to your healthcare provider right away if you reduce the amount of food or liquid you drink, for example if you are sick or cannot eat, or start to lose liquids from your body, for example from vomiting, diarrhea or being in the sun too long.

Other Medicines & Empagliflozin and Metformin combination

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Empagliflozin and Metformin combination may affect the way other medicines work, and other medicines may affect how Empagliflozin and Metformin combination works.

Especially tell your healthcare provider if you take:

- insulin or other medicines that can lower your blood sugar
- diuretics (water pills)

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

3. How to take Empagliflozin and Metformin

- Take Empagliflozin and Metformin combination exactly as your healthcare provider tells you to take it.
- Take Empagliflozin and Metformin combination by mouth two times each day with meals. Taking Empagliflozin and Metformin combination with meals may lower your chance of having an upset stomach.
- Your healthcare provider may change your dose if needed.
- Your healthcare provider may tell you to take Empagliflozin and Metformin combination along with other diabetes medicines. Low blood sugar can happen more often when Empagliflozin and Metformin combination is taken with certain other diabetes medicines.
- Your healthcare provider will do blood tests to check how well your kidneys are working before and during your treatment with Empagliflozin and Metformin combination.
- When taking Empagliflozin and Metformin combination, you may have sugar in your urine, which will show up on a urine test.

If you miss a dose. take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take two doses of Empagliflozin and Metformin combination at the same time. Talk with your healthcare provider if you have questions about a missed dose.

If you take too much Empagliflozin and Metformin combination, call your healthcare provider or go to the nearest hospital emergency room right away.

4. Possible side effects

Empagliflozin and Metformin combination may cause serious side effects, including:

- ***Serious urinary tract infections.*** Serious urinary tract infections that may lead to hospitalization have happened in people who are taking empagliflozin, one of the medicines in Empagliflozin and Metformin combination. Tell your healthcare provider if you have any signs or symptoms of a urinary tract infection such as a burning feeling when passing urine, a need to urinate often, the need to urinate right away, pain in the lower part of your stomach (pelvis), or blood in the urine. Sometimes people also may have a fever, back pain, nausea or vomiting.
- ***Low blood sugar (hypoglycemia).*** If you take Empagliflozin and Metformin combination with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take Empagliflozin and Metformin combination. Signs and symptoms of low blood sugar may include:
  - headache
  - irritability
  - confusion
  - dizziness
  - drowsiness
  - hunger
  - shaking or feeling jittery
  - sweating
  - weakness o fast heartbeat
- **A rare but serious bacterial infection that causes damage to the tissue under the skin *(necrotizing fasciitis)*** in the area between and around the anus and genitals (perineum). Necrotizing fasciitis of the perineum has happened in women and men who take empagliflozin, one of the medicines in Empagliflozin and Metformin combination. Necrotizing fasciitis of the perineum may lead to hospitalization, may require multiple surgeries, and may lead to death. Seek medical attention immediately if you have a fever or you are feeling very weak, tired or uncomfortable (malaise), and you develop any of the following symptoms in the area between and around your anus and genitals:
  - pain or tenderness
  - swelling
  - redness of skin (erythema)
- ***Vaginal yeast infection.*** Symptoms of a vaginal yeast infection include vaginal odor, white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese), or vaginal itching.
- ***Yeast infection of the penis (balanitis or balanoposthitis).*** Swelling of an uncircumcised penis may develop that makes it difficult to pull back the skin around the tip of the penis. Other symptoms of yeast infection of the penis include redness, itching, or swelling of the penis, rash of the penis, foul smelling discharge from the penis, or pain in the skin around the penis.

Talk to your healthcare provider about what to do if you get symptoms of a yeast infection of the vagina or penis. Your healthcare provider may suggest you use an over-the-counter antifungal medicine. Talk to your healthcare provider right away, if you use an over-the-counter antifungal medication and your symptoms do not go away.

- ***Allergic (hypersensitivity) reactions.*** Serious allergic reactions have happened in people who are taking empagliflozin, one of the medicines in Empagliflozin and Metformin combination. Symptoms may include:
  - swelling of your face, lips, throat and other areas of your skin
  - difficulty with swallowing or breathing
  - raised, red areas on your skin (hives)

  If you have any of these symptoms, stop taking Empagliflozin and Metformin combination and call your healthcare provider right away or go to the nearest hospital emergency room.
- ***Low vitamin B12 (vitamin B12 deficiency).*** Using metformin for long periods of time may cause a decrease in the amount of vitamin B12 in your blood, especially if you have had low vitamin B12 blood levels before. Your healthcare provider may do blood tests to check your vitamin B12 levels.

The most common side effects of Empagliflozin and Metformin combination include:

- low blood sugar
- gas
- urinary tract infection
- stomach discomfort
- stuffy or runny nose and sore throat
- indigestion
- yeast infections in females
- weakness
- diarrhea
- headache
- nausea or vomiting

These are not all the possible side effects of Empagliflozin and Metformin combination. For more information, ask your healthcare provider or pharmacist.

5. How to store Empagliflozin and Metformin

Store Empagliflozin and Metformin combination at room temperature between 20°C to 25°C.

Keep Empagliflozin and Metformin combination and all medicines out of the reach of children.

6. Contents of the pack and other information

What Empadil M contains:

The active ingredient is

EMPADIL M 5/500 (Empagliflozin and Metformin Hydrochloride Tablets 5/500 mg)
Each film coated tablet contains:

Empagliflozin IH	5 mg
Metformin Hydrochloride USP	500 mg
Excipients	q.s.

EMPADIL M 5/1000 (Empagliflozin and Metformin Hydrochloride Tablets 5/1000 mg)
Each film coated tablet contains:

Empagliflozin IH	5 mg
Metformin Hydrochloride USP	1000 mg
Excipients	q.s.

EMPADIL M 12.5/500 (Empagliflozin and Metformin Hydrochloride Tablets 12.5/500 mg)
Each film coated tablet contains:

Empagliflozin IH	12.5mg
Metformin Hydrochloride USP	500 mg
Excipients	q.s.

EMPADIL M 12.5/1000 (Empagliflozin and Metformin Hydrochloride Tablets 12.5/1000 mg)
Each film coated tablet contains:

Empagliflozin IH	12.5mg
Metformin Hydrochloride USP	1000 mg
Excipients	q.s.

List of Excipients:

EMPADIL M 5/500 (Empagliflozin and Metformin Hydrochloride Tablets 5/500 mg)
Crospovidone, Hydroxypropyl Cellulose, Mannitol, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Purified Water, Opadry 03F52025 Yellow IH.

EMPADIL M 5/1000 (Empagliflozin and Metformin Hydrochloride Tablets 5/1000 mg)
Crospovidone, Hydroxypropyl Cellulose, Mannitol, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Purified Water, Opadry 03F52025 Yellow IH.

EMPADIL M 12.5/500 (Empagliflozin and Metformin Hydrochloride Tablets 12.5/500 mg)
Crospovidone, Hydroxypropyl Cellulose, Mannitol, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Purified Water, Opadry 03B94681 Pink IH.

EMPADIL M 12.5/1000 (Empagliflozin and Metformin Hydrochloride Tablets 12.5/1000 mg)
Crospovidone, Hydroxypropyl Cellulose, Mannitol, Microcrystalline Cellulose, Colloidal Silicon Dioxide, Magnesium Stearate, Purified Water, Opadry 03B94681 Pink IH.

What Empadil M looks like and contents of the pack

EMPADIL M 5/500 (Empagliflozin and Metformin Hydrochloride Tablets 5/500 mg)
Yellow coloured, oval shaped, biconvex, film-coated tablets, debossed "EM" on one side and "1" on other side

EMPADIL M 5/1000 (Empagliflozin and Metformin Hydrochloride Tablets 5/1000 mg)
Yellow coloured, oval shaped, biconvex, film-coated tablets, debossed "EM" on one side and "2" on other side.

EMPADIL M 12.5/500 (Empagliflozin and Metformin Hydrochloride Tablets 12.5/500 mg)
Pink coloured, oval shaped, biconvex, film coated tablets, debossed "EM" on one side and "7" on other side.

EMPADIL M 12.5/1000 (Empagliflozin and Metformin Hydrochloride Tablets 12.5/1000 mg)
Pink coloured, oval shaped, biconvex, film coated tablets, debossed "EM" on one side and "7" on other side.

For any information about this medicinal product, please contact Manufacturing Authorization Holder.

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Manufacturing Authorization Holder	Manufacturer
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