

1. Generic Name and Brand Name

Empagliflozin 12.5 mg & Metformin Hydrochloride 500 mg Tablets

Empixel™-M 12.5/500

Empagliflozin 12.5 mg & Metformin Hydrochloride 1000 mg Tablets

Empixel™-M 12.5/1000

WARNING: LACTIC ACIDOSIS

- Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL
- Risk factors include renal impairment, concomitant use of certain drugs, age ≥65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high-risk groups are provided.
- If lactic acidosis is suspected, discontinue Empagliflozin and Metformin Hydrochloride Tablets and institute general supportive measures in a hospital setting. Prompt haemodialysis is recommended.

2. Qualitative and quantitative composition

Empixel™-M 12.5/500

Each film coated tablet contains:

Empagliflozin 12.5 mg

Metformin Hydrochloride IP 500 mg

Excipients q.s.

Colors: Ferric Oxide USP-NF Red, Ferrosoferric Oxide USP-NF Black and Titanium Dioxide IP

Empixel™-M 12.5/1000

Each film coated tablet contains:

Empagliflozin 12.5 mg

Metformin Hydrochloride IP 1000 mg

Excipients q.s.

Colors: Ferric Oxide USP-NF Red, Ferrosoferric Oxide USP-NF Black and Titanium Dioxide IP

3. Dosage form and strength

Refer section 1 & 2.

4. Clinical particulars

4.1. Therapeutic indication

It is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus who are not adequately controlled on a regimen containing empagliflozin or Metformin, or in patients already being treated with both empagliflozin and Metformin.

4.2. Posology and method of administration

Posology

- The maximum recommended total daily dose is 25 mg Empagliflozin and 2000 mg Metformin Hydrochloride.
- Metformin Hydrochloride used in these products is in Immediate Release form.
- Take twice daily with meals; with gradual dose escalation to reduce the gastrointestinal side effects due to metformin.
- Adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of Metformin hydrochloride 2000 mg and Empagliflozin 25 mg.
- Assess renal function prior to initiation of Empagliflozin and Metformin Hydrochloride Tablets and periodically, thereafter.
- Empagliflozin and Metformin Hydrochloride Tablets is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m²

Adults with normal renal function (eGFR $\geq$ 90 mL/min/1.73 m²)

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

For patients insufficiently controlled on metformin (either alone or in combination with other medicinal products for the treatment of diabetes)

In patients insufficiently controlled on metformin alone or in combination with other medicinal products for the treatment of diabetes, the recommended starting dose of Empagliflozin and Metformin Tablet should provide empagliflozin 5 mg twice daily (10 mg daily dose) and the dose of metformin similar to the dose already being taken. In patients tolerating a total daily dose of empagliflozin 10 mg and who need tighter glycaemic control, the dose can be increased to a total daily dose of empagliflozin 25 mg. When Empagliflozin and Metformin Tablet is used in combination with a Sulphonylurea and/or insulin, a lower dose of Sulphonylurea and/or insulin may be required to reduce the risk of hypoglycemia.

For patients switching from separate tablets of empagliflozin and metformin

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

Special populations

Renal impairment

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

For dose adjustment recommendations according to eGFR or CrCL refer to Table.

A eGFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

If no adequate strength of Empagliflozin and Metformin Tablet is available, individual mono components should be used instead of the fixed dose combination.

Table: Posology for renally impaired patients

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

Hepatic impairment

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

Elderly

Due to the mechanism of action, decreased renal function will result in reduced glycaemic efficacy of empagliflozin. Because metformin is excreted by the kidney and elderly patients are more likely to have decreased renal function, Empagliflozin and Metformin Tablet should be used with caution in these patients. Monitoring of renal function is necessary to aid in prevention of metformin-

associated lactic acidosis, particularly in elderly patients. In patients 75 years and older, an increased risk for Volume depletion should be taken into account.

Paediatric population

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

Method of administration

Tablets may be administered with or without food. The tablets must be swallowed with a glass of water. For oral use.

4.3. Contraindication

Empagliflozin and Metformin Hydrochloride Tablets are contraindicated in patients with:

- Moderate to severe renal impairment (eGFR less than 45 mL/min/1.73 m²), end stage renal disease, or dialysis
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- History of serious hypersensitivity reaction to Empagliflozin or Metformin.

4.4. Special warnings and precautions for use

Lactic acidosis

Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensive, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis.

Patients and/or caregivers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (<7.35), increased plasma lactate levels (>5 mmol/l) and an increased anion gap and lactate/pyruvate ratio.

Diabetic ketoacidosis

Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including empagliflozin. In a number of cases,

the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/l (250 mg/dl). It is not known if DKA is more likely to occur with higher doses of empagliflozin.

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

In patients where DKA is suspected or diagnosed, treatment with empagliflozin should be discontinued immediately.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with empagliflozin may be restarted when the ketone values are normal, and the patient's condition has stabilised.

Before initiating empagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.

Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g. type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients.

Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved. Empagliflozin and Metformin Tablet should not be used in patients with type 1 diabetes. Data from a clinical trial program in patients with type 1 diabetes showed increased DKA occurrence with common frequency in patients treated with empagliflozin 10mg and 25mg as an adjunct to insulin compared to placebo.

Administration of iodinated contrast agent

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

Renal impairment

Due to the mechanism of action, decreased renal function will result in reduced glycaemic efficacy of empagliflozin.

Empagliflozin/metformin is contraindicated in patients with $\text{eGFR} < 30 \text{ ml/min/1.73 m}^2$ and should be temporarily discontinued in the presence of conditions that alter renal function.

Monitoring of renal function

Assessment of renal function is recommended as follows:

- Prior to empagliflozin/metformin initiation and periodically during treatment, i.e. at least yearly.
- Prior to initiation of any concomitant medicinal product that may have a negative impact on renal function.

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, Empagliflozin and Metformin Tablet may be used with a regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, Empagliflozin and Metformin Tablet is contraindicated due to the metformin component.

Surgery

Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Risk for Volume depletion.

Based on the mode of action of SGLT2 inhibitors, osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in blood pressure. Therefore, caution should be exercised in patients for whom a empagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or patients aged 75 years and older.

In case of conditions that may lead to fluid loss (e.g. gastrointestinal illness), careful monitoring of Volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving Empagliflozin and Metformin Tablet. Temporary interruption of treatment with Empagliflozin and Metformin Tablet should be considered until the fluid loss is corrected.

Elderly

The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the hydration status. Patients aged 75 years and older may be at an increased risk of volume depletion. Therefore, special attention should be given to their volume intake in case of co-administered medicinal products which may lead to volume depletion (e.g. diuretics, ACE inhibitors).

Urinary tract infections

Post-marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin. Temporary interruption of treatment should be considered in patients with complicated urinary tract infections.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Post-marketing cases of necrotising fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Empagliflozin and Metformin Tablet should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Lower limb amputations

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

Hepatic injury

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

Elevated haematocrit

Haematocrit increase was observed with empagliflozin treatment.

Chronic kidney disease

There is experience with empagliflozin for the treatment of diabetes in patients with chronic kidney disease ($\text{eGFR} \geq 30\text{mL/min/1.73 m}^2$) both with and without albuminuria. Patients with albuminuria may benefit more from treatment with empagliflozin.

Urine laboratory assessments

Due to its mechanism of action, patients taking Empagliflozin and Metformin Tablet will test positive for glucose in their urine.

Interference with 1,5-anhydroglucitol (1,5-AG) assay

Monitoring glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Use of alternative methods to monitor glycaemic control is advised.

Vitamin B12

Metformin may reduce vitamin B12 levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anaemia or

neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contra-indicated.

4.5. Drugs interactions

Empagliflozin

Diuretics

Co-administration of Empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.

Insulin or Insulin Secretagogues

Co-administration of Empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycaemia.

Positive Urine Glucose Test

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

Pharmacokinetic interactions

Effects of other medicinal products on empagliflozin

In *vitro* data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by uridine 5'diphosphoglucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT287. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP181, and OATP183, but not OAT1 and OCT2. Empagliflozin is a substrate of Pglycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Co-administration of empagliflozin with probenecid, an inhibitor of UGT enzymes and OAT3, resulted in a 26% increase in peak empagliflozin plasma concentrations (C_{max}) and a 53% increase in area under the concentration-time curve (AUC). These changes were not considered to be clinically meaningful.

The effect of UGT induction (e.g. induction by rifampicin or phenytoin) on empagliflozin has not been studied. Cotreatment with known inducers of UGT enzymes is not recommended due to a potential risk of decreased efficacy. If an inducer of these UGT enzymes must be co-administered, monitoring of glycaemic control to assess response to Empagliflozin and Metformin Tablet is appropriate.

An interaction study with gemfibrozil, an *in vitro* inhibitor of OAT3 and OATP181/183 transporters, showed that empagliflozin C_{max} increased by 15% and AUC increased by 59% following co-administration. These changes were not considered to be clinically meaningful.

Inhibition of OATP181/183 transporters by co-administration with rifampicin resulted in a 75% increase in C_{max} and a 35% increase in AUC of empagliflozin. These changes were not considered to be clinically meaningful.

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

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

Effects of empagliflozin on other medicinal products

Empagliflozin may increase renal lithium excretion and the blood lithium levels may be decreased. Serum concentration of lithium should be monitored more frequently after empagliflozin initiation and dose changes. Please refer the patient to the lithium prescribing doctor in order to monitor serum concentration of lithium.

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

Empagliflozin does not inhibit P-gp at therapeutic doses. Based on *in vitro* studies, empagliflozin is considered unlikely to cause interactions with active substances that are P-gp substrates. Co-administration of digoxin, a P-gp substrate, with empagliflozin resulted in a 6% increase in AUC and 14% increase in C_{max} of digoxin. These changes were not considered to be clinically meaningful.

Empagliflozin does not inhibit human uptake transporters such as OAT3, OATP1 B1, and OATP1 B3 *in vitro* at clinically relevant plasma concentrations and, as such, drug-drug interactions with substrates of these uptake transporters are considered unlikely.

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

Metformin Hydrochloride

Drugs that Reduce Metformin Clearance

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. Consider the benefits and risks of concomitant use.

Carbonic Anhydrase Inhibitors

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. Concomitant use of these drugs with Empagliflozin and Metformin Tablets may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients.

Drugs Affecting Glycemic Control

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

Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving Empagliflozin and Metformin Tablets.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

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

Limited available data with Empagliflozin and Metformin Tablets 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.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

When the patient plans to become pregnant, and during pregnancy, it is recommended that diabetes is not treated with this medicinal product, but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the foetus associated with abnormal blood glucose levels.

Clinical Considerations Disease-associated maternal and/or embryo/foetal risk: Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth, and delivery complications. Poorly controlled diabetes increases the foetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data

Human Data

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

Animal Data

Empagliflozin:

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

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

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

Metformin hydrochloride:

Metformin hydrochloride did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits at up to 600 mg/kg/day during the period of

organogenesis. This represents an exposure of approximately 2- and 6-times a clinical dose of 2000 mg, based on body surface area (mg/m²) for rats and rabbits, respectively.

Empagliflozin and Metformin hydrochloride:

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

Lactation

Risk Summary

There is no information regarding the presence of Empagliflozin and Metformin hydrochloride or empagliflozin 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. However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. 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, advise women that use of Empagliflozin and Metformin hydrochloride is not recommended while breastfeeding.

Data

Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

Empagliflozin was present at a low level in rat fetal tissues after a single oral dose to the dams at gestation day 18. In rat milk, the mean milk to plasma ratio ranged from 0.634 -5 and was greater than one from 2 to 24 hours post-dose. The mean maximal milk to plasma ratio of 5 occurred at 8 hours post-dose, suggesting accumulation of empagliflozin in the milk. Juvenile rats directly exposed to empagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

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.

Paediatric Use

Safety and effectiveness of Empagliflozin and Metformin in pediatric patients under 18 years of age have not been established.

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.

Empagliflozin

No empagliflozin dosage change is recommended based on age. In studies assessing the efficacy of empagliflozin in improving glycemic control in patients with type 2 diabetes, a total of 2721 (32%) patients treated with empagliflozin were 65 years of age and older, and 491 (6%) were 75 years of age and older. Empagliflozin is expected to have diminished glycemic efficacy in elderly patients with renal impairment.

The risk of volume depletion-related adverse reactions increased in patients who were 75 years of age and older to 2.1%, 2.3%, and 4.4% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg. The risk of urinary tract infections increased in patients who were 75 years of age and older to 10.5%, 15.7%, and 15.1% in patients randomized to placebo, empagliflozin 10 mg, and Empagliflozin 25 mg, respectively.

Metformin hydrochloride

Controlled clinical studies of metformin hydrochloride did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients.

Renal Impairment

Empagliflozin and Metformin is contraindicated in patients with moderate to severe renal impairment (eGFR less than 45 mL/min/1.73 m²).

Empagliflozin: The efficacy and safety of empagliflozin have not been established in patients with severe renal impairment, with ESRD, or receiving dialysis. Empagliflozin is not expected to be effective in these patient populations. The glucose lowering benefit of Empagliflozin 25 mg decreased in patients with worsening renal function. The risks of renal impairment, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function.

Empagliflozin may be used in patients with an eGFR greater than or equal to 45 mL/min/1.73 m². Empagliflozin is not recommended in patients with an eGFR less than 45 mL/min/1.73 m². Metformin hydrochloride Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Empagliflozin and Metformin is contraindicated in moderate to severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 45 mL/min/1.73 m².

Hepatic Impairment

Empagliflozin and Metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Empagliflozin may be used in patients with hepatic impairment. 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.

4.7. Effects on ability to drive and use machines

Empagliflozin and Metformin Tablet has minor influence on the ability to drive and use machines. Patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines, in particular when Empagliflozin and Metformin Tablet is used in combination with a Sulphonylurea and/or insulin.

4.8. Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in clinical trials were hypoglycaemia in combination with insulin and/or Sulphonylurea and gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain and loss of appetite). No additional adverse reactions were identified in clinical trials with empagliflozin as add-on to metformin compared to the side effects of the single components.

Tabulated list of adverse reactions

The adverse reactions are listed by absolute frequency. Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), or very rare ($< 1/10,000$), and not known (cannot be estimated from the available data).

Table: Tabulated list of adverse reactions (MedDRA) from placebo- controlled studies and from post-marketing experience

System organ class	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations		Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection ^{1,2} Urinary tract infection (including pyelonephritis and urosepsis) ^{1,2}		Necrotising fasciitis of the perineum (Fournier's gangrene) ^a	

Metabolism and nutrition disorders	Hypoglycaemia (when used with sulphonylureas or insulin) ¹	Thirst ² Vitamin B12 decrease/deficiency ^{3, a}		Diabetic ketoacidosis ^a	Lactic acidosis ³
Nervous system disorders		Taste disturbance ³			
Vascular disorders			Volume depletion ^{1,2,d}		
Gastrointestinal disorders	Gastrointestinal symptoms ^{3,4}	Constipation			
Hepatobiliary disorders					Liver function tests abnormalities ³ Hepatitis ³
Skin and subcutaneous tissue disorders		Pruritus (generalized) ^{2,3} Rash	Urticaria Angioedema		Erythema ³
Renal and urinary disorders		Increased urination ^{1, 2}	Dysuria ²		Tubulointerstitial nephritis
Investigations		Serum lipids increased ^{2,b}	Blood creatinine increased/Glomerular filtration rate decreased ¹ Haematocrit increased ^{2, c}		

1 See subsections below for additional information

2 Identified adverse reactions of empagliflozin monotherapy

3 Identified adverse reactions of metformin monotherapy

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

a See section 4.4

b Mean percent increases from baseline for empagliflozin 10 mg and 25 mg versus placebo respectively, were total cholesterol 5.0% and 5.2% versus 3.7%; HDL-cholesterol 4.6% and 2.7% versus -0.5% ; LDL-cholesterol 9.1% and 8.7% versus 7.8%; triglycerides 5.4% and 10.8% versus 12.1%.

c Mean changes from baseline in haematocrit were 3.6% and 4.0% for empagliflozin 10 mg and 25 mg respectively, compared to 0% for placebo. In the EMPA-REG Outcome study, haematocrit values returned towards baseline values after a follow-up period of 30 days after treatment stop.

d Pooled data of empagliflozin trials in patients with heart failure (where half of the patients had type 2 diabetes mellitus) showed a higher frequency of volume depletion ("very common" : 11.4% for empagliflozin versus 9. 7% for placebo)

Empagliflozin

Adverse Reactions Reported in $\geq 5\%$ of Patients Treated with Empagliflozin

Hypoglycemia, Urinary tract infection, Female genital mycotic infections, Upper respiratory tract infection, increased urination, Dyslipidemia, Arthralgia, Male genital mycotic infections, Nasopharyngitis and Nausea.

Metformin HCl

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

4.9. Overdose

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

Metformin hydrochloride

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

5. Pharmacological properties

5.1. Mechanism of action

Empagliflozin

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

Metformin Hydrochloride

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 day-long plasma insulin response may actually decrease.

5.2. Pharmacodynamic properties

Empagliflozin:

Urinary Glucose Excretion

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

Urinary Volume

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

Cardiac Electrophysiology

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

Metformin:

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT) known to date.

In humans, independently of its action on glycaemia, metformin has favorable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term, or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

5.3. Pharmacokinetic properties

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 C_{max} were 1870 nmol·h/L and 259 nmol/L, respectively, with 10 mg Empagliflozin once daily treatment, and 4740 nmol·h/L and 687 nmol/L, respectively, with 25 mg Empagliflozin once daily treatment. Systemic exposure of Empagliflozin increased in a dose proportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of Empagliflozin were similar, suggesting linear pharmacokinetics with respect to time.

Distribution

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

Metabolism

No major metabolites of Empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite was less than 10% of total drug-related material. In vitro studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Excretion

The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state, which was consistent with empagliflozin half-life. Following administration of an oral [14C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%). The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

Metformin Hydrochloride:

Absorption

The absolute bioavailability of a metformin hydrochloride 500-mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin 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 C_{max}, a 25% lower AUC, and a 35-minute prolongation of time to peak plasma concentration (T_{max}) 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.

Metabolism

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

Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin hydrochloride tablets 850 mg averaged 654±358 L. Metformin is negligibly

bound to plasma proteins, in contrast to SUs, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride tablets, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally.

Excretion

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

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Empagliflozin

Carcinogenesis

Carcinogenesis was evaluated in 2-year studies conducted in CD-1 mice and Wistar rats. Empagliflozin did not increase the incidence of tumors in female rats dosed at 100, 300, or 700 mg/kg/day (up to 72 times the exposure from the maximum clinical dose of 25 mg). In male rats, hemangiomas of the mesenteric lymph node were increased significantly at 700 mg/kg/day or approximately 42 times the exposure from a 25 mg clinical dose.

Empagliflozin did not increase the incidence of tumors in female mice dosed at 100, 300, or 1000 mg/kg/day (up to 62 times the exposure from a 25 mg clinical dose). Renal tubule adenomas and carcinomas were observed in male mice at 1000 mg/kg/day, which is approximately 45 times the exposure of the maximum clinical dose of 25 mg. These tumours may be associated with a metabolic pathway predominantly present in the male mouse kidney.

Mutagenesis

Empagliflozin was not mutagenic or clastogenic with or without metabolic activation in the in vitro Ames bacterial mutagenicity assay, the in vitro L5178Y tk[±] mouse lymphoma cell assay, and an in vivo micronucleus assay in rats.

Impairment of Fertility

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

Metformin Hydrochloride

Carcinogenesis

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended

human daily dose of 2000 mg/kg/day based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

Mutagenesis

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

Impairment of Fertility

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

7. Description

Empixel™ M 12.5/500

Pale brownish purple colored, oval shape, biconvex, film coated tablets, plain on both sides.

Empixel™ M 12.5/1000

Dark brownish purple, colored, oval shape, biconvex, film coated tablets, plain on both sides.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not Applicable

8.2. Shelf-life

Refer pack.

8.3. Packaging information

Refer pack.

8.4. Storage and handling instructions

Refer pack.

9. Patient Counselling Information

What is the most important information I should know about Empagliflozin and Metformin Tablets?

Empagliflozin and Metformin Tablets is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both Empagliflozin and Metformin hydrochloride is appropriate.

Before taking Empagliflozin and Metformin tablets, tell your doctor about all of your medical conditions, including:

- have moderate to severe kidney problems
- have liver problems
- have a history of urinary tract infection or problems with urination
- have heart problems, including congestive heart failure
- are going to have surgery
- are eating less due to illness, surgery, or 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 a lot of alcohol in the short term (“binge” drinking)
- are going to get an injection of dye or contrast agents for an x-ray procedure.

How should I take Empagliflozin and Metformin Tablets?

- Take Empagliflozin and Metformin Tablets exactly as your doctor tells you to take it.
- Taking Empagliflozin and Metformin with a meal may lower your chance of having an upset stomach.
- Take Empagliflozin and Metformin Tablets whole. Do not break, cut, crush, dissolve, or chew Empagliflozin and Metformin tablets before swallowing. If you cannot swallow Empagliflozin and Metformin tablets whole, tell your doctor.
- You may see something that looks like the Empagliflozin and Metformin Tablets in your stool (bowel movement). If you see tablets in your stool talk to your doctor. Do not stop taking Empagliflozin and Metformin without talking to your doctor.
- Your doctor will tell you how much Empagliflozin and Metformin to take and when to take it.
- Your doctor may change your dose if needed.
- 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 Tablet at the same time. Talk with your doctor if you have questions about a missed dose.
- Your doctor may tell you to take Empagliflozin and Metformin along with other diabetes medicines.

“What are the possible side effects of Empagliflozin and Metformin Tablets?”

- If you take too much Empagliflozin and Metformin Tablets, call your doctor or go to the nearest hospital emergency room right away.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine that you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor’s instructions.
- Check your blood sugar as your doctor tells you to.
- When taking Empagliflozin and Metformin Tablets, you may have sugar in your urine, which will show up on a urine test.
- Stay on your prescribed diet and exercise program while taking Empagliflozin and Metformin Tablets.

- Talk to your doctor about how to prevent, recognize and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and complications of diabetes.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.
- Your doctor will do blood tests to check how well your kidneys are working before and during your treatment with Empagliflozin and Metformin Tablets.
- Your doctor may do certain blood tests before you start Empagliflozin and Metformin Tablets and during treatment.

10. Details of manufacturer

Refer pack for manufacturer details.

Marketed by:

Abbott Healthcare Pvt. Ltd.

Angel Space, Bldg. D-4, Gala No. 1 to 3 & 11 to 13 Ground Floor,
101 to 106 & 111 to 116 First Floor, 201 to 206 & 211 to 216 2nd Floor,
Pimplas, Dist. Thane, Bhiwandi-421 302, Maharashtra, India.

11. Details of permission or licence number with date

Refer Pack for Permission/License details.

12. Date of revision

Version 1.0 dated 12-Feb-25

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For product complaints and queries please write to
webmasterindia@abbott.com