FloriMet®

Empagliflozin / Metformin Hydrochloride

FORMS AND PRESENTATION

FloriMet®5/1000: Film Coated Tablets: Box of 60.

FloriMet®12.5/1000: Film Coated Tablets: Box of 60.

COMPOSITION

FloriMet®5/1000: Each Film Coated Tablet contains Empagliflozin 5 mg and Metformin Hydrochloride 1000mg.

FloriMet®12.5/1000: Each Film Coated Tablet contains Empagliflozin 12.5 mg and Metformin Hydrochloride 1000mg.

Excipients: corn starch, povidone, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol, talc, iron oxide yellow (FloriMet®5/1000), iron oxide red (FloriMet®12.5/1000), black iron oxide (FloriMet®12.5/1000).

PHARMACOLOGICAL PROPERTIES

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

Pharmacodynamic properties

Mechanism of action

FloriMet® combines two antihyperglycemic medicinal products with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: empagliflozin, an inhibitor of sodium-glucose co-transporter 2 (SGLT2), and metformin hydrochloride, a member of the biguanide class.

Empagliflozin

Empagliflozin is a reversible, highly potent, and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2). Empagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 5 000 times more selective for SGLT2 versus SGLT1, the major transporter responsible for glucose absorption in the gut. SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible, as the predominant transporter, for the reabsorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes and hyperglycaemia a higher amount of glucose is filtered and reabsorbed.

Empagliflozin improves glycemic control in patients with type 2 diabetes by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent on blood glucose concentration and GFR. Inhibition of SGLT2 in patients with type 2 diabetes and hyperglycaemia leads to excess glucose excretion in the urine. Increased urinary glucose excretion results in an immediate reduction in plasma glucose levels in patients with type 2 diabetes. In addition, initiation of empagliflozin increases excretion of sodium resulting in osmotic diuresis and reduced intravascular volume.

Empagliflozin improves both fasting and post-prandial plasma glucose levels. The mechanism of action of empagliflozin is independent of beta cell function and insulin pathway and this contributes to a low risk of hypoglycemia.

In addition, urinary glucose excretion triggers calorie loss, associated with body fat loss and body weight reduction. The glucosuria observed with empagliflozin is accompanied by mild diuresis which may contribute to sustained and moderate reduction of blood pressure. The glucosuria, natriuresis and osmotic diuresis observed with empagliflozin may contribute to the improvement in cardiovascular outcomes.

Metformin

Metformin is a biguanide with antihyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia. Metformin may act via 3 mechanisms:

- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis,
- in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization,
- and delay of intestinal glucose absorption.

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

In humans, independently of its action on glycaemia, metformin has favorable effects on lipid metabolism, by reducing total cholesterol, LDL cholesterol and triglyceride levels.

Pharmacokinetic properties

FloriMet®5/1000 and FloriMet®12.5/1000 combination tablets are bioequivalent to co-administration of corresponding doses of empagliflozin and metformin as individual tablets.

Empagliflozin

Absorption

After oral administration, empagliflozin is rapidly absorbed with peak plasma concentrations occurring at a median t_{max} of 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 with empagliflozin 10 mg and 4740 nmol.h/l and 687 nmol/l with empagliflozin 25 mg once daily. Systemic exposure of empagliflozin increased in a dose-proportional manner. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar suggesting linear pharmacokinetics with respect to time. There were no clinically relevant differences in empagliflozin pharmacokinetics between healthy volunteers and patients with type 2 diabetes.

Administration of empagliflozin 25 mg after intake of a high-fat and high calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and C_{max} 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. Similar results were obtained when empagliflozin/metformin combination tablets were administered with high-fat and high calorie meal.

Distribution

The apparent steady-state volume of distribution was estimated to be 73.8 L based on the population pharmacokinetic analysis. Following administration of an oral [^{14}C]-empagliflozin solution to healthy volunteers, the red blood cell partitioning was approximately 37% and plasma protein binding was 86%.

Biotransformation

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

Elimination

Based on the population pharmacokinetic analysis, the apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 hours and apparent oral clearance was 10.6 l/hour. With once-daily dosing, steady-state plasma concentrations of empagliflozin were reached by the fifth dose. Consistent with the half-life, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state. Following the administration of an oral [^{14}C]-empagliflozin solution to healthy volunteers, approximately 96% was eliminated in faeces (41%) or urine (54%). The majority of drug-related radioactivity recovered in faeces was unchanged parent drug and approximately half of drug related radioactivity excreted in urine was unchanged parent drug.

Special populations

Renal impairment

In patients with mild, moderate, or severe renal impairment (eGFR <30 - <90 ml/min/1.73 m^2) and patients with kidney failure/end stage renal disease (ESRD), AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. The population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure.

Hepatic impairment

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

Pediatric population

The observed pharmacokinetic and pharmacodynamic responses, in children and adolescents between 10 and 18 years of age with type 2 diabetes mellitus, were consistent with those found in adult subjects.

Metformin

Absorption

After an oral dose of metformin, t_{max} is reached in 2.5 hours. Absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in feces was 20-30%. After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption are non-linear. At the recommended metformin doses and dosing schedules, steady-state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 microgram/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 5 microgram/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin.

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (Vd) ranged between 63 - 276 l.

Biotransformation

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination

Renal clearance of metformin is >400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Special populations

Paediatric population

After single doses of metformin hydrochloride 500 mg, paediatric patients have shown a similar pharmacokinetic profile to that observed in healthy adults.

After repeated doses of 500 mg twice daily for 7 days in paediatric patients the peak plasma concentration (C_{max}) and systemic exposure (AUC_{0-t}) were approximately 33% and 40% lower, respectively, compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days.

INDICATIONS

FloriMet® is indicated in adults and children aged 10 years and above for the treatment of type 2 diabetes mellitus as an adjunct to diet and exercise:

- in patients insufficiently controlled on their maximally tolerated dose of metformin alone
- in combination with other medicinal products for the treatment of diabetes, in patients insufficiently controlled with metformin and these medicinal products
- in patients already being treated with the combination of empagliflozin and metformin as separate tablets.

CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).
- Diabetic pre-coma.
- Severe renal failure (eGFR <30 ml/min/1.73 m^2).
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock.
- Disease which may cause tissue hypoxia (especially acute disease or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock.
- Hepatic impairment, acute alcohol intoxication, alcoholism.

PRECAUTIONS

FloriMet® should not be used for treatment of patients with type 1 diabetes.

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 healthcare professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, 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 who previously experienced diabetic ketoacidosis (DKA) while taking an SGLT2 inhibitor is not recommended unless a specific and correctable cause for the DKA has been identified and addressed.

Administration of an 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. FloriMet® is contraindicated in patients with eGFR<30 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 FloriMet® 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, FloriMet® may be used with a regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, FloriMet® 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 an 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 FloriMet®. Temporary interruption of treatment 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

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)

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, FloriMet® 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 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 (eGFR ≥30 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 FloriMet® 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

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 contraindicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

Paediatric population

The overall safety profile in children and adolescents was similar with the known safety profile seen in adult patients. No effect of metformin on growth and puberty has been detected but no long-term data are available. Therefore, a careful follow-up of the effect of metformin on these parameters in metformin-treated children, especially prepubescent children, is recommended.

Children aged between 10 and 12

Caution is recommended when prescribing to children aged between 10 and 12 years.

Effects on ability to drive and use machines

FloriMet® has minor influence on the ability to drive and use machines. Patients should be advised to take precautions to avoid hypoglycemia while driving and using machines, in particular when this treatment is used in combination with a sulphonylurea and/or insulin.

PREGNANCY AND LACTATION

Pregnancy

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.

Breast-feeding

Metformin is excreted into human milk. A risk to the newborns/infants cannot be excluded.

This medicinal product should not be used during breast feeding.

DRUG INTERACTIONS

Co-administration of multiple doses of empagliflozin and metformin does not meaningfully alter the pharmacokinetics of either empagliflozin or metformin in healthy subjects.

The following statements reflect the information available on the individual active substances.

Empagliflozin

Pharmacodynamic interactions

Diuretics

Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

Insulin and insulin secretagogues

Insulin and insulin secretagogues, such as sulphonylureas, may increase the risk of hypoglycemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with empagliflozin.

Pharmacokinetic interactions

Effects of other medicinal products on empagliflozin

In vitro data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by uridine 5'-diphospho-glucuronosyltransferase UGT1A3, UGT1A8, UGT1A9, and UGT2B7. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Co-treatment 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 glycemic control to assess response to empagliflozin is appropriate.

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

Effects of empagliflozin on other medicinal products

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 to monitor serum concentration of lithium.

Drug-drug interactions involving the major CYP450 and UGT isoforms with empagliflozin and concomitantly administered substrates of these enzymes are 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.

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

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

Metformin

Concomitant use not recommended

Alcohol

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

Organic cation transporters (OCT)

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

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

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

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

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

Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

Iodinated contrast agents

Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

Combination requiring precautions for use

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Glucocorticoids (given by systemic and local routes), beta 2 agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment with such medicinal products. If necessary, the dose of the anti hyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

Insulin and insulin secretagogues

Insulin and insulin secretagogues, such as sulphonylureas, may increase the risk of hypoglycemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with metformin.

ADVERSE EFFECTS

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

Infections and infestations: vaginal moniliasis, vulvovaginitis, balanitis and other genital infections, urinary tract infection including pyelonephritis and urosepsis (common); necrotizing fasciitis of the perineum (Fournier's gangrene) (rare).

Metabolism and nutrition disorders: hypoglycemia when used with sulfonylurea or insulin (very common); thirst, vitamin B12 decrease/deficiency (common); diabetic ketoacidosis (rare); lactic acidosis (very rare).

Nervous system disorders: taste disturbance (common).

Gastrointestinal Disorders: gastrointestinal symptoms (very common); constipation (common).

Skin and subcutaneous tissue disorders: generalized pruritis, rash (common); urticaria, angioedema (uncommon); erythema (very rare).

Vascular disorders: volume depletion (uncommon).

Renal and urinary disorders: increased urination (common); dysuria (uncommon); tubule-interstitial nephritis (very rare).

Hepatobiliary disorders: liver function tests abnormalities, hepatitis (very rare).

Investigations: increase in serum lipids (common); increase in blood creatinine, increase in hematocrit, decrease in glomerular filtration rate (uncommon).

DOSAGE AND ADMINISTRATION

Posology

Adults with normal renal function (eGFR ≥90 ml/min/1.73 m^2)

The recommended dose is one tablet twice daily. The dosage should be individualised based on 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 these patients, the recommended starting dose of FloriMet® 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 FloriMet® 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 FloriMet® should receive the same daily dose of empagliflozin and metformin already being taken or the nearest therapeutically appropriate dose of metformin.

Missed dose

If a dose is missed, it should be taken as soon as the patient remembers; however, a double dose should not be taken on the same time. In that case, the missed dose should be skipped.

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 m^2 (see table below). 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 the table below.

An 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 FloriMet® 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 m^2] 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, FloriMet® 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 considered.

Paediatric population

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

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

If patients switching from separate tablets of empagliflozin and metformin to FloriMet® the same daily dose of empagliflozin and metformin should remain as already being taken or the nearest therapeutically appropriate dose of metformin.

The maximum recommended daily dose of FloriMet® is 25 mg of empagliflozin and 2000 mg of metformin.

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

Method of administration

FloriMet® should be taken twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin. The tablets should be swallowed whole with water. All patients should continue their diet with an adequate distribution of carbohydrate intake during the day. Overweight patients should continue their energy restricted diet.

OVERDOSAGE

Empagliflozin

Single doses of up to 800 mg empagliflozin (equivalent to 32-times the highest recommended daily dose) in healthy patients and multiple daily doses of up to 100 mg empagliflozin (equivalent to 4-times the highest recommended daily dose) in patients with type 2 diabetes did not show any toxicity. Empagliflozin increased urine glucose excretion leading to an increase in urine volume. The observed increase in urine volume was not dose-dependent and is not clinically meaningful. There is no experience with doses above 800 mg.

Metformin

Hypoglycemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital.

Therapy

In the event of an overdose, treatment should be initiated as appropriate to the patient's clinical status. The most effective method to remove lactate and metformin is hemodialysis. The removal of empagliflozin by hemodialysis has not been studied.

STORAGE CONDITIONS

Store below 30°C.

Date of Revision: August 2025

Marketing Authorization Holder and Manufacturer

Benta SAL

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BPI

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