# Floriance®

## Empagliflozin

**FORMS AND PRESENTATION**

Floriance®10: Film Coated Tablets: Box of 30.
Floriance®25: Film Coated Tablets: Box of 30.

**COMPOSITION**

Floriance®10: Each Film Coated Tablet contains Empagliflozin 10 mg.
Floriance®25: Each Film Coated Tablet contains Empagliflozin 25 mg.
Excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, colloidal silicon dioxide, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol, talc, iron oxide yellow.

**PHARMACOLOGICAL PROPERTIES**

Pharmacotherapeutic group: Drugs used in diabetes, Sodium-glucose co-transporter 2 (SGLT2) inhibitors, ATC code: A10BK03

***Pharmacodynamic properties***

Mechanism of action

Empagliflozin is a reversible, highly potent ($IC_{50}$ of 1.3 nmol), 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 hyperglycemia a higher amount of glucose is filtered and reabsorbed.
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 hyperglycemia leads to excess glucose excretion in the urine. In addition, initiation of empagliflozin increases excretion of sodium resulting in osmotic diuresis and reduced intravascular volume.
In patients with type 2 diabetes, urinary glucose excretion increased immediately following the first dose of empagliflozin and is continuous over the 24-hour dosing interval.
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.
Empagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to: increasing tubuloglomerular feedback and reducing intraglomerular pressure, lowering both pre- and afterload of the heart, downregulating of sympathetic activity and reducing left ventricular wall stress as evidenced by lower NT-proBNP values which may have beneficial effects on cardiac remodeling, filling pressures and diastolic function as well as preserving kidney structure and function. Other effects such as an increase in hematocrit, a reduction in body weight and blood pressure may further contribute to the beneficial cardiac and renal effects.

***Pharmacokinetic properties***

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 Cmax were 1 870 nmol.h/l and 259 nmol/l with empagliflozin 10 mg and 4 740 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 Cmax 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 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 and the most abundant metabolites were three glucuronide conjugates (2-, 3-, and 6-O glucuronide). Systemic exposure of each metabolite was less than 10% of the total drug-related material. *In vitro* studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'- diphospho- glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Elimination

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. 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.

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 %23 ,%4, 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.

**INDICATIONS**

Floriance is indicated for:
-Type 2 Diabetes Mellitus in adults and children aged 10 years and above:
• As monotherapy when metformin is inappropriate due to intolerance.
• As an add-on to other diabetes treatments.
-Heart Failure: Treatment of symptomatic chronic heart failure in adults.
-Chronic Kidney Disease: Treatment of chronic kidney disease in adults..

**CONTRAINDICATIONS**

Empagliflozin is contraindicated in the case of hypersensitivity to the active substance or to any of the excipients.

**PRECAUTIONS**

Empagliflozin should not be used in patients with type 1 diabetes mellitus.

Ketoacidosis

Cases of ketoacidosis, including life-threatening and fatal cases, have been reported in patients with diabetes mellitus 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 ketoacidosis is more likely to occur with higher doses of empagliflozin. Although ketoacidosis is less likely to occur in patients without diabetes mellitus, cases have also been reported in these patients.
The risk of 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 ketoacidosis is suspected or diagnosed, treatment with empagliflozin should be discontinued immediately.
Treatment should be interrupted in patients who are hospitalized 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 stabilized.
Before initiating empagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.
Patients who may be at higher risk of ketoacidosis 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 ketoacidosis while on SGLT2 inhibitor treatment is not recommended unless another clear precipitating factor is identified and resolved.

Renal impairment

Due to limited experience, it is not recommended to initiate treatment with empagliflozin in patients with an eGFR <20 ml/min/1.73 m$^2$.
In patients with an eGFR <60 ml/min/1.73 m$^2$ the daily dose of empagliflozin is 10 mg.
The glucose lowering efficacy of empagliflozin is dependent on renal function, and is reduced in patients with an eGFR <45 ml/min/1.73 m$^2$ and is likely absent in patients with an eGFR <30 ml/min/1.73 m$^2$

*Monitoring of renal function*

Assessment of renal function is recommended as follows:
- Prior to empagliflozin 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.

Risk for volume depletion

Based on the mode of action of SGLT2 inhibitors, osmotic diuresis accompanying 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 hematocrit) and electrolytes is recommended for patients receiving empagliflozin. Temporary interruption of treatment with empagliflozin 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. A higher number of these patients treated with empagliflozin had adverse reactions related to volume depletion as compared to placebo Therefore, special attention should be given to their volume intake in case of co-administered medicinal products.

Complicated urinary tract infections

Cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin. Temporary interruption of empagliflozin should be considered.

Necrotizing fasciitis of the perineum (Fournier's gangrene)

Cases of necrotizing fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients with diabetes mellitus 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 urogenital infection or perineal abscess may precede necrotizing fasciitis. If Fournier's gangrene is suspected, empagliflozin should be discontinued and prompt treatment 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. A causal relationship between empagliflozin and hepatic injury has not been established.

Elevated hematocrit

Hematocrit increase was observed with empagliflozin treatment.

Chronic kidney disease

Patients with albuminuria may benefit more from treatment with empagliflozin.

Urine laboratory assessments

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

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 of alternative methods to monitor glycemic control is advised.

Lactose

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Sodium

Each tablet contains less than 1 mmol sodium (23 mg), that is to say essentially 'sodium free'.

**Effects on ability to drive and use machines**

Empagliflozin 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 empagliflozin is used in combination with a sulphonylurea and/or insulin.

**PREGNANCY AND LACTATION**

Pregnancy

There are no data from the use of empagliflozin in pregnant women. As a precautionary measure, it is preferable to avoid the use of empagliflozin during pregnancy.

Breast-feeding

A risk to the newborns/infants cannot be excluded. Empagliflozin should not be used during breast-feeding.

**DRUG INTERACTIONS**

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'-diphosphoglucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Co-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 glycaemic control to assess response to Floriance is appropriate.

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

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

*Effects of empagliflozin on other medicinal products*

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.

Based on in vitro studies, empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. Empagliflozin is unlikely to cause drug-drug interactions involving CYP450 and UGT isoforms. It does not inhibit P-gp or human uptake transporters such as OAT3, OATP1B1, and OATP1B3 at clinically relevant plasma concentrations.

Empagliflozin has no clinically significant effect on the pharmacokinetics of commonly used drugs, including metformin, glimepiride, sitagliptin, pioglitazone, linagliptin, simvastatin, ramipril, digoxin, warfarin, diuretics and oral contraceptives.

**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 (common); diabetic ketoacidosis (uncommon).

*Gastrointestinal Disorders*: constipation (common).

*Skin and subcutaneous tissue disorders*: pruritis, rash (common); urticaria, angioedema (uncommon).

*Vascular disorders*: volume depletion (very common).

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

*Type 2 diabetes mellitus*

The recommended starting dose is 10 mg empagliflozin once daily for monotherapy and add-on combination therapy with other medicinal products for the treatment of diabetes. In patients tolerating empagliflozin 10 mg once daily who have an eGFR ≥60 ml/min/1.73 $m^2$ and need tighter glycemic control, the dose can be increased to 25 mg once daily. The maximum daily dose is 25 mg.

*Heart failure*

The recommended dose is 10 mg empagliflozin once daily.

*All indications*

When empagliflozin is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycemia.

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 day.

Special populations

*Renal impairment*

Due to limited experience, it is not recommended to initiate treatment with empagliflozin in patients with an eGFR <20 ml/min/1.73 $m^2$.

In patients with an eGFR <60 ml/min/1.73 $m^2$ the daily dose of empagliflozin is 10 mg.

In patients with type 2 diabetes mellitus, the glucose lowering efficacy of empagliflozin is reduced in patients with an eGFR <45 ml/min/1.73 $m^2$ and likely absent in patients with an eGFR <30 ml/min/1.73 $m^2$. Therefore, if eGFR falls below 45 ml/min/1.73 $m^2$, additional glucose lowering treatment should be considered if needed.

*Hepatic impairment*

No dose adjustment is required for patients with hepatic impairment. Empagliflozin exposure is increased in patients with severe hepatic impairment. Therapeutic experience in patients with severe hepatic impairment is limited and therefore not recommended for use in this population.

*Elderly*

No dose adjustment is recommended based on age. In patients 75 years and older, an increased risk for volume depletion should be considered.

*Pediatric population*

The recommended starting dose is 10 mg empagliflozin once daily. In patients tolerating empagliflozin 10 mg once daily and requiring additional glycemic control, the dose can be increased to 25 mg once daily. No data are available for children with eGFR <60 ml/min/1.73 $m^2$ and children below 10 years of age.

The safety and efficacy of empagliflozin in children and adolescents has not yet been established.

Method of administration

The tablets can be taken with or without food.

**OVERDOSAGE**

Symptoms

In controlled clinical studies single doses of up to 800 mg empagliflozin in healthy volunteers and multiple daily doses of up to 100 mg empagliflozin in patients with type 2 diabetes did not show any toxicity. Empagliflozin increased urine glucose excretion leading to an increase in urine volume. The observed increase in urine volume was not dose-dependent and is not clinically meaningful. There is no experience with doses above 800 mg in humans.

Therapy

In the event of an overdose, treatment should be initiated as appropriate to the patient's clinical status. The removal of empagliflozin by hemodialysis has not been studied.

**STORAGE CONDITIONS**

Store below 30°C.

**Date of Revision:** November 2024

**Marketing Authorization Holder & Manufacturer:**

Benta S.A.L

Dbayeh-Lebanon

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