



FLICTAMET

XR Tablets

Composition

Flictamet XR 5/1000 Tablets

Each extended-release tablet contains Dapagliflozin 5mg and metformin HCl 1000 mg.

Flictamet XR 10/1000 Tablets

Each extended-release tablet contains Dapagliflozin 10mg and metformin HCl 1000 mg.

Action

FLICTAMET XR combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: Dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and metformin hydrochloride, a biguanide.

Dapagliflozin

Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, Dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

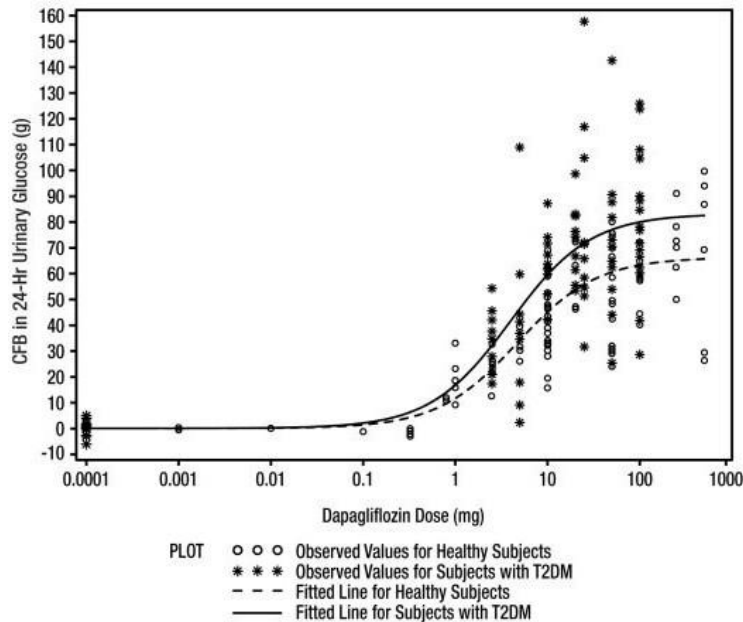
Metformin hydrochloride

Metformin improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not produce hypoglycemia in either patient with type 2 diabetes or in healthy subjects, except in unusual 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.

Pharmacodynamics

Dapagliflozin

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following the administration of Dapagliflozin (see Figure below). Dapagliflozin doses of 5 or 10 mg per day in patients with type 2 diabetes mellitus for 12 weeks resulted in excretion of approximately 70 grams of glucose in the urine per day. A near maximum glucose excretion was observed at the Dapagliflozin daily dose of 20 mg. This urinary glucose excretion with Dapagliflozin also results in increases in urinary volume.



Scatter Plot and Fitted Line of Change from Baseline in 24-Hour Urinary Glucose Amount versus Dapagliflozin Dose in Healthy Subjects and Subjects with Type 2 Diabetes Mellitus (T2DM) (Semi-Log Plot)

Cardiac Electrophysiology

Dapagliflozin was not associated with clinically meaningful prolongation of QTc interval at daily doses up to 150 mg (15 times the recommended dose) in a study of healthy subjects. In addition, no clinically meaningful effect on QTc interval was observed following single doses of up to 500 mg (50 times the recommended dose) Dapagliflozin in healthy subjects.

Pharmacokinetics

FLICTAMET XR combination tablets are considered to be bioequivalent to administration of corresponding doses of Dapagliflozin (INFLICTA) and metformin hydrochloride extended-release (GLUCOMET XR) administered together as individual tablets.

The administration of FLICTAMET XR in healthy subjects after a standard meal compared to the fasted state resulted in the same extent of exposure for both Dapagliflozin and metformin extended-release.

Compared to the fasted state, the standard meal resulted in 35% reduction and a delay of 1 to 2 hours in the peak plasma concentrations of Dapagliflozin. This effect of food is not considered to be clinically meaningful. Food has no relevant effect on the pharmacokinetics of metformin when administered as FLICTAMET XR combination tablets.

Absorption

Dapagliflozin

Following oral administration of Dapagliflozin, the maximum plasma concentration (C_{max}) is usually attained within 2 hours under fasting state. The C_{max} and AUC values increase dose proportionally with increase in Dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of Dapagliflozin following the administration of a 10 mg dose is 78%. Administration of Dapagliflozin with a high-fat meal decreases its C_{max} by up to 50% and prolongs T_{max} by approximately 1 hour, but



does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful and Dapagliflozin can be administered with or without food.

Metformin hydrochloride

Following a single oral dose of metformin extended-release, C_{max} is achieved with a median value of 7 hours and a range of 4 to 8 hours. The extent of metformin absorption (as measured by AUC) from the

metformin extended-release tablet increased by approximately 50% when given with food. There was no effect of food on C_{max} and T_{max} of metformin.

Distribution

Dapagliflozin

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with renal or hepatic impairment.

Metformin hydrochloride

Distribution studies with extended-release metformin have not been conducted; however, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes.

Metabolism

Dapagliflozin

The metabolism of Dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield Dapagliflozin 3- O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% of a 50 mg [14 C]-Dapagliflozin dose and is the predominant drug-related component in human plasma.

Metformin hydrochloride

Intravenous single-dose studies in healthy subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

Metabolism studies with extended-release metformin tablets have not been conducted.

Elimination

Dapagliflozin

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [14 C]-Dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life ($t_{1/2}$) for Dapagliflozin is approximately 12.9 hours following a single oral dose of Dapagliflozin 10 mg.



Metformin hydrochloride

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.

Specific Populations

Renal Impairment

Dapagliflozin

At steady-state (20 mg once-daily Dapagliflozin for 7 days), patients with type 2 diabetes with mild, moderate, or severe renal impairment (as determined by eGFR) had geometric mean systemic exposures of Dapagliflozin that were 45%, 2.04 fold, and 3.03-fold higher, respectively, as compared to patients with type 2 diabetes with normal renal function. Higher systemic exposure of Dapagliflozin in patients with type 2 diabetes mellitus with renal impairment did not result in a correspondingly higher

24-hour glucose excretion. The steady-state 24-hour urinary glucose excretion in patients with type 2 diabetes and mild, moderate, and severe renal impairment was 42%, 80%, and 90% lower, respectively, than in patients with type 2 diabetes with normal renal function. The impact of hemodialysis on Dapagliflozin exposure is not known.

Metformin hydrochloride

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged, and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Because FLICTAMET XR contains metformin, FLICTAMET XR should generally be avoided in patients with hepatic impairment

Dapagliflozin

In patients with mild and moderate hepatic impairment (Child-Pugh Classes A and B), mean C_{max} and AUC of Dapagliflozin were up to 12% and 36% higher, respectively, as compared to healthy matched control subjects following single-dose administration of 10 mg Dapagliflozin. These differences were not considered to be clinically meaningful. In patients with severe hepatic impairment (Child-Pugh Class C), mean C_{max} and AUC of Dapagliflozin were up to 40% and 67% higher, respectively, as compared to healthy matched controls.

Metformin hydrochloride

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.



Geriatric

Dapagliflozin

Based on a population pharmacokinetic analysis, age does not have a clinically meaningful effect on systemic exposures of Dapagliflozin; thus, no dose adjustment is recommended.

Metformin hydrochloride

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggests that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatric

Pharmacokinetics in the pediatric population has not been studied.

Body Weight

Dapagliflozin

Based on a population pharmacokinetic analysis, body weight does not have a clinically meaningful effect on systemic exposures of Dapagliflozin; thus, no dose adjustment is recommended.

Indications

FLICTAMET XR (Dapagliflozin and metformin HCl extended-release) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both Dapagliflozin and metformin is appropriate.

Limitations of Use

FLICTAMET XR is not recommended for patients with type 1 diabetes mellitus or diabetic ketoacidosis.

Contraindications

- Severe renal impairment (eGFR below 30 mL/min/1.73 m² end stage renal disease or patients on dialysis).
- History of a serious hypersensitivity reaction to Dapagliflozin or hypersensitivity to metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Warnings & Precautions

Lactic Acidosis

There have been post-marketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence, however, hypothermia, hypotension, and resistant bradyarrhythmias have accorded with severe acidosis.



Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations ($>5\text{mmol/L}$), anion gap acidosis (without evidence of (ketonuria or ketonemia), and an increased lactate: pyruvate ratio; metformin plasma levels generally $>5\text{ mcg/mL}$. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis especially in patients at risk.

If metformin, associated lactic acidosis is suspected, general supportive measures should be instituted. promptly in a hospital setting, along with immediate discontinuation of FLICTAMET XR.

In FLICTAMET XR-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin. (metformin HCl is dialyzable, with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery

Hypoxic States: Several of the post marketing cases of metformin- associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue FLICTAMET XR.

Excessive Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin associated lactic acidosis. Warn patients against excessive alcohol intake while receiving FLICTAMET XR.

Hepatic Impairment: Patients with hepatic impairment have developed with cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of FLICTAMET XR in patients with clinical or laboratory evidence of hepatic disease.

Hypotension

Dapagliflozin causes intravascular volume contraction. Symptomatic hypotension can occur after initiating Dapagliflozin, particularly in patients with impaired renal function (eGFR less than 60

mL/min/1.73 m^2), elderly patients, or patients on loop diuretics. Before initiating FLICTAMET XR in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms of hypotension after initiating therapy.

Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in post marketing surveillance in patients with type 1 and type 2 diabetes mellitus taking sodium glucose co-transporter-2 (SGLT2) inhibitors, including Dapagliflozin. FLICTAMET XR is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with FLICTAMET XR who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of blood glucose levels as ketoacidosis associated with FLICTAMET XR may be present even if blood glucose levels are less



than 250 mg/dL. If ketoacidosis is suspected, FLICTAMET XR should be discontinued, the patient should be evaluated and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and the institution of treatment was delayed because the presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating FLICTAMET XR, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction and alcohol abuse. For patients who undergo scheduled surgery, consider temporarily discontinuing FLICTAMET XR for at least 3 days prior to surgery.

consider monitoring for ketoacidosis and temporarily discontinuing FLICTAMET XR in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting FLICTAMET XR.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue FLICTAMET XR and seek medical attention immediately if signs and symptoms occur.

Acute Kidney Injury and Impairment in Renal Function

Dapagliflozin causes intravascular volume contraction, and can cause acute kidney injury. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving Dapagliflozin. some reports involved patients younger than 65 years of age.

Before initiating FLICTAMET XR, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing FLICTAMET XR in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue FLICTAMET XR promptly and institute treatment.

Dapagliflozin increases serum creatinine and decreases eGFR. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Adverse reactions related to renal function can occur after initiating FLICTAMET XR. Renal function should be evaluated prior to initiation of FLICTAMET XR and monitored periodically thereafter.



Use of FLICTAMET XR is not recommended when the eGFR is less than 45 mL/min/1.73 m².

FLICTAMET XR is contraindicated in patients with an eGFR below 30 mL/min/1.73 m².

Urosepsis and Pyelonephritis

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

Use with Medications Known to Cause Hypoglycemia

Dapagliflozin

Insulin and insulin secretagogues are known to cause hypoglycemia. Dapagliflozin can increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with FLICTAMET XR.

Metformin hydrochloride

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking betaadrenergic blocking drugs.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier's Gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including Dapagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with FLICTAMET XR presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue FLICTAMET XR, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Vitamin B₁₂ Concentrations

In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B₁₂ levels, without clinical manifestations, was observed in approximately 7% of patients. This decrease, possibly due to interference with B₁₂ absorption from the B₁₂-intrinsic factor complex is, however, very rarely associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B₁₂ supplementation. Measurement of



hematologic parameters on an annual basis is advised in patients on FLICTAMET XR and any apparent abnormalities should be appropriately investigated and managed.

Certain individuals (those with inadequate vitamin B₁₂ or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B₁₂ levels. In these patients, routine serum vitamin B₁₂ measurements at 2- to 3-year intervals may be useful.

Genital Mycotic Infections

Dapagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat appropriately.

Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Dapagliflozin in pregnant women. Studies in rats treated with Dapagliflozin have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy. Therefore, the use of this medicinal product is not recommended during the second and third trimesters of pregnancy. A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development.

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

It is unknown whether this medicinal product or Dapagliflozin (and/or its metabolites) are excreted in human milk. Available Pharmacodynamic/toxicological data in animals have shown excretion of Dapagliflozin/metabolites in milk, as well as pharmacologically-mediated effects in nursing offspring. Metformin is excreted in human milk in small amounts. A risk to the newborns/infants cannot be excluded. This medicinal product should not be used while breast-feeding.

Fertility

The effect of this medicinal product or Dapagliflozin on fertility in humans has not been studied. In male and female rats, Dapagliflozin showed no effects on fertility at any dose tested. For metformin, studies in animals have not shown reproductive toxicity.

Adverse Reactions

The following adverse reactions have been identified in the placebo-controlled Dapagliflozin plus metformin clinical studies, Dapagliflozin clinical studies and metformin clinical studies and post-

marketing experience. None were found to be dose-related. Adverse reactions listed below are classified according to frequency and system organ class. Frequency categories are defined according to the following convention: 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 $< 1/1,000$), very rare ($< 1/10,000$), and not known (cannot be estimated from the available data).

Adverse reactions in Dapagliflozin and metformin clinical trial and post-marketing data^a

System organ class	Very common	Common	Uncommon	Rare	Very rare
<i>Infections and infestations</i>		Vulvovaginitis, balanitis and related genital infections ^{*,b,c} Urinary tract infection ^{*,b,d}	Fungal infection ^{**}		Necrotising fasciitis of the perineum (Fournier's gangrene) ^{b,k}
<i>Metabolism and nutrition disorders</i>	Hypoglycaemia (when used with SU or insulin) ^p		Volume depletion ^{b,e} Thirst ^{**}	Diabetic ketoacidosis ^{b,k,l}	Lactic acidosis Vitamin B12 deficiency ^{h,s}
<i>Nervous system disorders</i>		Taste disturbance [§] Dizziness			
<i>Gastrointestinal disorders</i>	Gastrointestinal symptoms ^{i,§}		Constipation ^{**} Dry mouth ^{**}		
<i>Hepatobiliary disorders</i>					Liver function disorders [§] Hepatitis [§]
<i>Skin and subcutaneous tissue disorders</i>		Rash ^m			Urticaria [§] Erythema [§] Pruritus [§]
<i>Musculoskeletal and connective tissue disorders</i>		Back pain [†]			
<i>Renal and urinary disorders</i>		Dysuria Polyuria ^{*,f}	Nocturia ^{**}		
<i>Reproductive system and breast disorders</i>			Vulvovaginal pruritus ^{**} Pruritus genital ^{**}		
<i>Investigations</i>		Haematocrit increased ^g	Blood creatinine increased		

		Creatinine renal clearance decreased during initial treatment ^b Dyslipidaemia ^j	during initial treatment ^{**b} Blood urea increased ^{**} Weight decreased ^{**}		
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^aThe table shows adverse reactions identified from up to 24-week (short-term) data regardless of glycaemic rescue.

^bSee corresponding subsection below for additional information.

^cVulvovaginitis, balanitis and related genital infections includes, e.g. the predefined preferred terms: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess.

^dUrinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis.

^eVolume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia, hypotension.

^fPolyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.

^gMean changes from baseline in haematocrit were 2.30% for Dapagliflozin 10 mg versus -0.33% for placebo. Haematocrit values >55% were reported in 1.3% of the subjects treated with Dapagliflozin 10 mg versus 0.4% of placebo subjects.

^hLong-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B12 deficiency (e.g. megaloblastic anaemia).

ⁱGastrointestinal 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.

^jMean percent change from baseline for Dapagliflozin 10 mg versus placebo, respectively, was: total cholesterol 2.5% versus 0.0%; HDL cholesterol 6.0% versus 2.7%; LDL cholesterol 2.9% versus -1.0%; triglycerides -2.7% versus -0.7%.

^kSee Warnings.

^lReported in the cardiovascular outcomes study in patients with type 2 diabetes. Frequency is based on annual rate.

^mAdverse reaction was identified through post-marketing surveillance with the use of Dapagliflozin. Rash includes the following preferred terms, listed in order of frequency in clinical trials: rash, rash generalized, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous.

ⁿReported in ≥ 2% of subjects and ≥ 1% more and at least 3 more subjects treated with Dapagliflozin 10 mg compared to placebo.

^{**}Reported by the investigator as possibly related, probably related or related to study treatment and reported in ≥ 0.2% of subjects and ≥ 0.1% more and at least 3 more subjects treated with Dapagliflozin 10 mg compared to placebo.

Drug Interactions

Coadministration of multiple doses of Dapagliflozin and metformin does not meaningfully alter the pharmacokinetics of either Dapagliflozin or metformin in healthy subjects. No interaction studies have been performed for the Combination. The following statements reflect the information available on the individual active substances.

Dapagliflozin

Pharmacodynamic interactions

Diuretics

This medicinal product 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, cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with Dapagliflozin.



Pharmacokinetic interactions

The metabolism of Dapagliflozin is primarily via glucuronide conjugation mediated by UDP-glucuronosyltransferase 1A9 (UGT1A9).

In *in vitro* studies, Dapagliflozin neither inhibited cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, nor induced CYP1A2, CYP2B6 or CYP3A4. Therefore, this medicinal product is not expected to alter the metabolic clearance of coadministered medicinal products that are metabolized by these enzymes.

Effect of other medicinal products on Dapagliflozin

Interaction studies conducted in healthy subjects, using mainly a single-dose design, suggest that the pharmacokinetics of Dapagliflozin are not altered by pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.

Following coadministration of Dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolizing enzymes) a 22% decrease in Dapagliflozin systemic exposure (AUC) was observed, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended. A clinically relevant effect with other inducers (e.g. carbamazepine, phenytoin, phenobarbital) is not expected.

Following coadministration of Dapagliflozin with mefenamic acid (an inhibitor of UGT1A9), a 55% increase in Dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended.

Effect of Dapagliflozin on other medicinal products

In interaction studies conducted in healthy subjects, using mainly a single-dose design, Dapagliflozin did not alter the pharmacokinetics of pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, digoxin (a P-gp substrate) or warfarin (S-warfarin, a CYP2C9 substrate), or the anti-coagulatory effects of warfarin as measured by INR. Combination of a single dose of Dapagliflozin 20 mg and simvastatin (a CYP3A4 substrate) resulted in a 19% increase in AUC of simvastatin and 31% increase in AUC of simvastatin acid. The increase in simvastatin and simvastatin acid exposures are not considered clinically relevant.

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.

Paediatric population

Interaction studies have only been performed in adults.

Metformin

Concomitant use not recommended



Cationic substances that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with metformin by competing for common renal tubular transport systems. A study conducted in seven normal healthy volunteers showed that cimetidine, administered as 400 mg twice daily, increased metformin systemic exposure (AUC) by 50% and C_{max} by 81%. Therefore, close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are coadministered.

Alcohol

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in the case of fasting, malnutrition or hepatic impairment due to the metformin active substance of this medicinal product. Consumption of alcohol and medicinal products containing alcohol should be avoided.

Iodinated contrast agents

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. Flictamet 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

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 glucose-lowering medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

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.

Insulin and insulin secretagogues

Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. 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.

Dosage and Administration

- Take FLICTAMET XR once daily in the morning with food with gradual dose escalation to reduce the gastrointestinal (GI) side effects due to metformin.
- Swallow FLICTAMET XR tablets whole and never crush, cut, or chew. Occasionally, the inactive ingredients of FLICTAMET XR will be eliminated in the feces as a soft, hydrated mass that may resemble the original tablet.
- Individualize the starting dose of XIGDUO XR based upon the patient's current regimen



- Dosing may be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 10 mg Dapagliflozin and 2000 mg metformin HCl.
- Patients taking an evening dose of metformin XR should skip their last dose before starting FLICTAMET XR.
- In patients with volume depletion, correcting this condition prior to initiation of FLICTAMET XR is recommended.

Patients with Renal Impairment

No dosage adjustment for FLICTAMET XR is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m². FLICTAMET XR is not recommended in patients with an eGFR below 45 mL/min/1.73 m².

Over Dosage

Dapagliflozin

There were no reports of overdose during the clinical development program for Dapagliflozin. In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ supportive measures as dictated by the patient's clinical status. The removal of Dapagliflozin by hemodialysis has not been studied.

Metformin hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts >50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

Presentation

FLIXTAMET XR Tablets are available in Boxes of 30 tablets.