# ZygloMet® XR

## Dapagliflozin / Metformin Hydrochloride XR

**FORMS AND PRESENTATION**
ZygloMet® XR 5/1000: Film coated tablets: Box of 60.
ZygloMet® XR 10/1000: Film coated tablets: Box of 30.
**COMPOSITION**
ZygloMet® XR 5/1000: Each film coated tablet contains Dapagliflozin 5mg and Metformin Hydrochloride equivalent to Metformin 1000mg as extended release.
ZygloMet® XR 10/1000: Each film coated tablet contains Dapagliflozin 10mg and Metformin Hydrochloride equivalent to Metformin 1000mg as extended release.
Excipients: Sodium carboxymethyl cellulose, hypromellose, microcrystalline cellulose, magnesium stearate, sodium lauryl sulfate, crospovidone, lactose monohydrate, silicon dioxide, iron oxide sicovit red, polyvinyl alcohol partially hydrolyzed, titanium dioxide, macrogol, talc, iron oxide red, black iron oxide.
**PHARMACOLOGICAL PROPERTIES**
Pharmacotherapeutic group: Drugs used in diabetes, Combinations of oral blood glucose-lowering drugs, ATC code: A10BD15.
Mechanism of action
Dapagliflozin / Metformin combines two anti-hyperglycemic medicinal products with different and complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: dapagliflozin, an SGLT2 inhibitor, and metformin hydrochloride, a member of the biguanide class.
***Pharmacodynamic properties***
*Dapagliflozin*
Dapagliflozin is a highly potent, selective, and reversible inhibitor of SGLT2.
The SGLT2 is selectively expressed in the kidney with no expression detected in other tissues including liver, skeletal muscle, adipose tissue, breast, bladder, and brain. SGLT2 is the predominant transporter responsible for the reabsorption of glucose from the glomerular filtrate back into circulation. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval, and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycemia. It acts independently of insulin secretion and insulin action. Improvement in homeostasis model assessment for beta cell function (HOMA beta-cell) has been observed in clinical studies with dapagliozin.
Urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with caloric loss and reduction in weight. Inhibition of glucose and sodium co-transport by dapagliflozin is also associated with mild diuresis and transient natriuresis. Evidence of sustained glucose excretion was seen in subjects with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years.
Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a sustained reduction in serum uric acid concentration.
Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is > 1,400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.
*Metformin*
Metformin is a biguanide with anti-hyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia.
Metformin may act via three mechanisms:
- by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis;
- by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilization in muscle;
- by delaying intestinal glucose absorption.
Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).
In humans, independently of its action on glycemia, metformin has favorable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term, or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol, and triglyceride levels.
In clinical studies, the use of metformin was associated with either stable body weight or modest weight loss.
***Pharmacokinetic properties***
Dapagliflozin
*Absorption*
Dapagliflozin is rapidly and well absorbed after oral administration. Maximum dapagliflozin plasma concentrations ($C_{max}$) were usually attained within 2 hours after administration in the fasted state. Geometric mean steady-state dapagliflozin $C_{max}$ and AUC values following once daily 10 mg doses of dapagliflozin were 158 ng/mL and 628 ng h/mL, respectively. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%.
*Distribution*
Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in various disease states (e.g. renal or hepatic impairment). The mean steady-state volume of distribution of dapagliflozin is 118 liters.
*Biotransformation*
Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP-mediated metabolism was a minor clearance pathway in humans.
*Elimination*
The mean plasma terminal half-life ($t_{1/2}$) for dapagliflozin was 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. The mean total systemic clearance of dapagliflozin administered intravenously was 207 mL/min. Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2% as unchanged dapagliflozin. After administration of a 50 mg [$^{14}$C]-dapagliflozin dose, 96% was recovered, 75% in urine, and 21% in feces. In feces, approximately 15% of the dose was excreted as parent drug.
*Special populations*
*Renal impairment*
At steady-state (20 mg once-daily dapagliflozin for 7 days), subjects with type 2 diabetes mellitus and mild, moderate, or severe renal impairment (as determined by iohexol plasma clearance) had mean systemic exposures of dapagliflozin of 32%, 60%, and 87% higher, respectively, than those of subjects with type 2 diabetes mellitus and normal renal function. The steady-state 24-hour urinary glucose excretion was highly dependent on renal function. The impact of hemodialysis on dapagliflozin exposure is not known.
*Hepatic impairment*
In subjects with mild or moderate hepatic impairment (Child-Pugh classes A and B), mean $C_{max}$ and AUC of dapagliflozin were up to 12% and 36% higher, respectively, compared with healthy matched control subjects. These differences were not considered to be clinically meaningful. In subjects with severe hepatic impairment (Child-Pugh class C) mean $C_{max}$ and AUC of dapagliflozin were 40% and 67% higher than matched healthy controls, respectively.
*Elderly (≥ 65 years)*
There is no clinically meaningful increase in exposure based on age alone in subjects up to 70 years old.
*Gender*
The mean dapagliflozin $AUC_{ss}$ in females was estimated to be about 22% higher than in males.
*Race*
There were no clinically relevant differences in systemic exposures between White, Black, or Asian races.
*Body weight*
Dapagliflozin exposure was found to decrease with increased weight. Consequently, low-weight patients may have somewhat increased exposure and patients with high weight somewhat decreased exposure. However, the differences in exposure were not considered clinically meaningful.
*Pediatric population*
Pharmacokinetics in the pediatric population has not been studied.
Metformin
*Absorption*
After an oral dose of metformin, $t_{max}$ is reached in 2.5 h. 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 is non-linear. At the usual metformin doses and dosing schedules, steady-state plasma concentrations are reached within 24-48 hours and are generally less than 1 µg/mL. In controlled clinical trials, maximum metformin plasma levels ($C_{max}$) did not exceed 5 µg/mL, even at maximum doses.
*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 $V_d$ 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.
*Special populations*
*Renal impairment*
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, leading to increased levels of metformin in plasma.
**INDICATIONS**
ZygloMet® XR is indicated in adults 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 dapagliflozin 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 (GFR < 30 mL/min).
- acute conditions with the potential to alter renal function such as dehydration, severe infection, and shock.
- acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, or shock.
- hepatic impairment.
- acute alcohol intoxication, alcoholism.
**PRECAUTIONS**
Lactic acidosis
Lactic acidosis 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 diarrhea or vomiting, fever, or reduced fluid intake), dapagliflozin / metformin should be temporarily discontinued and contact with a health care professional is recommended.
Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and non-steroidal anti-inflammatory drugs [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 care-givers should be informed on the risk of lactic acidosis.
Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking ZygloMet® XR and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (<7.35), increased plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio.
Renal function
The glycemic efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and is likely absent in patients with severe renal impairment. Dapagliflozin / metformin should not be initiated in patients with GFR < 60 mL/min and should be discontinued at GFR persistently below 45 mL/min. Metformin is excreted by the kidney, and moderate to severe renal insufficiency increases the risk of lactic acidosis.
Monitoring of renal function:
Renal function should be assessed:
• Before initiation of treatment and regularly thereafter.
• For renal function with GFR levels < 60 mL/min and in elderly patients, at least 2 to 4 times per year.
• Prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter.
• If renal function falls persistently below GFR 45 mL/min, treatment should be discontinued.
• Metformin is contraindicated in patients with GFR of < 30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function.
Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating anti-hypertensive or diuretic therapy or when starting treatment with a NSAID.
Use in patients at risk for volume depletion and/or hypotension
Due to its mechanism of action, dapagliflozin increases diuresis which may lead to the modest decrease in blood pressure observed in clinical studies. It may be more pronounced in patients with high blood glucose concentrations.
Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients on anti-hypertensive therapy with a history of hypotension or elderly patients.
In case of intercurrent conditions that may lead to volume depletion (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit and electrolytes) is recommended. Temporary interruption of treatment with this medicinal product is recommended for patients who develop volume depletion until the depletion is corrected.
Diabetic ketoacidosis
The risk of diabetic ketoacidosis (DKA) must be considered when using dapagliflozin. Patients should be assessed for ketoacidosis immediately, regardless of blood glucose level, if these symptoms occur: nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue, or sleepiness.
In patients where DKA is suspected or diagnosed, treatment with dapagliflozin should be discontinued immediately. Treatment should be interrupted in patients who are hospitalized for major surgical procedures or acute serious medical illnesses. Monitoring of blood ketones is recommended in these patients. Treatment with dapagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilized.
Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.

Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g. type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients. Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.
The safety and efficacy of dapagliflozin / metformin in patients with type 1 diabetes have not been established and it should not be used for the treatment of patients with type 1 diabetes. In type 1 diabetes mellitus studies, DKA was reported with a common frequency.
Necrotizing fasciitis of the perineum (Fournier's gangrene)
This is a rare but serious and potentially life-threatening event that requires discontinuation of dapagliflozin / metformin treatment and urgent surgical intervention with antibiotic treatment.
Patients should 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 necrotizing fasciitis. If Fournier's gangrene is suspected, ZygloMet® XR should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.
Urinary tract infections
Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of treatment should be considered when treating pyelonephritis or urosepsis.
Elderly (≥ 65 years)
Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics. They are more likely to have impaired renal function, and/or to be treated with anti-hypertensive medicinal products that may cause changes in renal function.
Cardiac failure
There is no experience in clinical studies with dapagliflozin in NYHA class IV.
Lower limb amputations
An increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term, clinical studies with another SGLT2 inhibitor. Like for all diabetic patients, it is important to counsel patients on routine preventative foot care.
*Urine laboratory assessments*
Due to its mechanism of action, patients taking this medicinal product will test positive for glucose in their urine.
*Administration of 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. ZygloMet® XR 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.
Surgery
ZygloMet® XR must be discontinued at the time of surgery with general, spinal, or epidural anesthesia. 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.
***Effects on ability to drive and use machines***
Dapagliflozin / metformin has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycemia when this medicinal product is used in combination with other glucose-lowering medicinal products known to cause hypoglycemia.

**PREGNANCY AND LACTATION**

Pregnancy
There are no data from the use of dapagliflozin / metformin in pregnant women. 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.
Breast-feeding
It is unknown whether this medicinal product is excreted in human milk. Available pharmacodynamic 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 breastfeeding.

**DRUG INTERACTIONS**

No interaction studies have been performed for dapagliflozin / metformin. 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*
The pharmacokinetics of dapagliflozin is not altered by pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.
Following coadministration of dapagliflozin with rifampicin 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, 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. The combination of a single dose of dapagliflozin 20 mg and simvastatin (a CYP3A4 substrate) resulted in an increase in AUC of simvastatin and simvastatin acid. The increase is not considered clinically relevant.
*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.
Metformin
*Concomitant use not recommended*
Close monitoring of glycemic 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 an increased risk of lactic acidosis. ZygloMet® XR 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, beta-2 agonists, and diuretics have intrinsic hyperglycemic activity. 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.
*Insulin and insulin secretagogues*
Insulin and insulin secretagogues, such as sulphonylureas, cause 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 dapagliflozin or metformin.

**ADVERSE EFFECTS**

Dapagliflozin / metformin has been demonstrated to be bioequivalent with coadministered dapagliflozin and metformin. There have been no therapeutic clinical trials conducted with combination tablets.
Adverse reactions listed below are classified according to frequency and system organ class. Frequency categories are defined according to the following convention: 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), very rare (< 1/10,000), and not known (cannot be estimated from the available data).
*Infections and infestations:* vulvovaginitis, balanitis, and related genital infections, urinary tract infection (common); fungal infection (uncommon); necrotizing fasciitis of the perineum (Fournier's gangrene) (very rare).
*Metabolism and nutrition disorders:* hypoglycemia (when used with SU or insulin) (very common); volume depletion, thirst (uncommon); diabetic ketoacidosis (rare); lactic acidosis, vitamin B12 deficiency (very rare).
*Nervous system disorders:* dizziness, taste disturbance (common).
*Gastrointestinal disorders:* gastrointestinal symptoms (very common); constipation, dry mouth (uncommon).
*Hepatobiliary disorders:* liver function disorders, hepatitis (very rare).
*Skin and subcutaneous tissue disorders:* rash (common); urticaria, erythema, pruritus (very rare).
*Musculoskeletal disorders:* back pain (common).
*Renal and urinary disorders:* dysuria, polyuria (common); nocturia (uncommon).
*Reproductive system and breast disorders:* vulvovaginal pruritus, pruritus genital (uncommon).
*Investigations:* hematocrit increased, creatinine renal clearance decreased during initial treatment, dyslipidemia (common); blood creatinine increase during initial treatment, blood urea increase, weight decrease (uncommon).

**DOSAGE AND ADMINISTRATION**

Posology
*Adults with normal renal function (glomerular filtration rate [GFR] ≥ 90 mL/min)*
The recommended dose of ZygloMet® XR 5/1000 is one tablet twice daily, the recommended dose of ZygloMet® XR 10/1000 is one tablet daily, or as prescribed by your physician.
Patients insufficiently controlled on metformin alone or in combination with other medicinal products for the treatment of diabetes should receive a total daily dose of ZygloMet® XR equivalent to dapagliflozin 10 mg, plus the total daily dose of metformin, or the nearest therapeutically appropriate dose, already being taken. When ZygloMet® XR is used in combination with insulin or an insulin secretagogue such as sulphonylurea, a lower dose of insulin or sulphonylurea may be considered to reduce the risk of hypoglycemia.
Patients switching from separate tablets of dapagliflozin (10 mg total daily dose) and metformin to ZygloMet® XR
These patients should receive the same daily dose of dapagliflozin and metformin already being taken or the nearest therapeutically appropriate dose of metformin.
*Special populations*
*Renal impairment*
A GFR should be assessed before initiation of treatment with metformin 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 (every 3-6 months).
The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis should be reviewed before considering the initiation of metformin in patients with GFR < 60 mL/min.
If no adequate strength of ZygloMet® XR is available, individual mono-components should be used instead of the combination.
*Hepatic impairment*
This medicinal product must not be used in patients with hepatic impairment.
*Elderly* (≥ 65 years)
Because metformin is eliminated in part by the kidney, and because elderly patients are more likely to have decreased renal function, this medicinal product should be used with caution as age increases.
*Pediatric population*
The safety and efficacy of ZygloMet® XR in children and adolescents aged 0 to < 18 years have not yet been established. No data are available.
Method of administration
ZygloMet® XR should be given with meals to reduce the gastrointestinal adverse reactions associated with metformin.

**OVERDOSAGE**

Removal of dapagliflozin by hemodialysis has not been studied. The most effective method to remove metformin and lactate is hemodialysis.
Dapagliflozin
Dapagliflozin did not show any toxicity in healthy subjects at single oral doses up to 50 times the maximum recommended human dose. These subjects had detectable glucose in the urine for a dose-related period of time, with no reports of dehydration, hypotension, or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycemia was similar to placebo.
In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.
Metformin
High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in a hospital.

**STORAGE CONDITIONS**

Store below 30˚C.
Keep in original pack in intact conditions.

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**Marketing Authorization Holder and Manufacturer**
**Benta** S.A.L.
Dbayeh – Lebanon

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