Front

XIGA Met™

[DAPAGLIFLOZIN+METFORMIN HCI]

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COMPOSITION:
XIGA Met 5/850 Tablet:
Each film coated tablet contains:
Dapagliflozin Propanediol monohydrate equivalent to
Dapagliflozin ..... 5 mg.
Metformin HCl ..... 850 mg.

Product Specs.: Innovator

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DESCRIPTION:
Dapagliflozin is a highly potent, selective and reversible inhibitor of SGLT2. The SGLT2 is selectively expressed in the kidney with no expression detected in more than 70 other tissues including liver, skeletal muscle, adipose tissue, breast, bladder and brain. SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Despite the presence of hyperglycaemia in type 2 diabetes, reabsorption of filtered glucose continues. 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) 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 hypoglycaemia. Dapagliflozin 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 dapagliflozin. 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. 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-hyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia. 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 utilisation 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).

CLINICAL PHARMACOLOGY:
Mechanism of Action:
XIGA Met combines two anti-hyperglycaemic medicinal products with different and complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: Dapagliflozin, a SGLT2 inhibitor, and metformin hydrochloride, a member of the biguanide class.
Pharmacodynamics:
Dapagliflozin: Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in sulects with type 2 diabetes mellitus. Following the administration of dapagliflozin. Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in subjects with type 2 diabetes mellitus for 12 weeks. Evidence of sustained glucose excretion was seen in subjects with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years. This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume in subjects with type 2 diabetes mellitus. Urinary volume increases in subjects with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and amounted to approximately 375 mL/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations. Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a sustained reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from-48.3 to -18.3 micromoles/L (-0.87 to-0.33 mg/dL). The pharmacodynamics of 5 mg dapagliflozin twice daily and 10 mg dapagliflozin once daily were compared in healthy subjects. The steady-state inhibition of renal glucose reabsorption and the amount of urinary glucose excretion over a 24-hour period was the same for both dosing regimens. Metformin in humans, independently of its action on glycaemia, has favourable 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, use of metformin was associated with either a stable body weight or modest weight loss. Clinical efficacy and safety The co-administration of dapagliflozin and metformin has been studied in subjects, with type 2 diabetes, inadequately controlled on diet and exercise alone, and in subjects inadequately controlled on metformin alone or in combination with a DPP-4 inhibitor (sitagliptin), sulphonylurea or insulin. Treatment with dapagliflozin plus metformin at all doses produced clinically relevant and statistically significant improvements in HbA1c and fasting plasma glucose (FPG) compared with control. Clinically relevant glycaemic effects were sustained in long-term extensions up to 104 weeks. HbA1c reductions were seen across subgroups including gender, age, race, duration of disease, and baseline body mass index (BMI).
Pharmacokinetics:
XIGA Met combination tablets are considered to be bioequivalent to co-administration of corresponding doses of dapagliflozin and metformin hydrochloride administered together as individual tablets. The pharmacokinetics of 5 mg dapagliflozin twice daily and 10 mg dapagliflozin once daily were compared in healthy subjects. Administration of 5 mg dapagliflozin twice daily gave similar overall exposures (AUCs) over a 24-hour period as 10 mg dapagliflozin administered once daily. As expected, dapagliflozin 5 mg administered twice daily compared with 10 mg dapagliflozin once daily resulted in lower peak dapagliflozin plasma concentrations (C_{max}) and higher trough plasma dapagliflozin concentrations (C_{min}).
Interaction with food: The administration of this medicinal product in healthy volunteers after a high fat meal compared to after the fasted state resulted in the same extent of exposure for both dapagliflozin and metformin. The meal resulted in a delay of 1 to 2 hours in the peak concentrations and a decrease in the maximum plasma concentration of 29% of dapagliflozin and 17% of metformin. These changes are not considered to be clinically meaningful.
Paediatric population: Pharmacokinetics in the paediatric population have not been studied. The following statements reflect the pharmacokinetic properties of the individual active substances of this medicinal product.
Absorption: Dapagliflozin was 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_T 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 was not altered in various disease states (e.g. renal or hepatic impairment). The mean steady-state volume of distribution of dapagliflozin was 118 liters.
Biotransformation: Dapagliflozin is extensively metabolised, 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 UGT1 A9, 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 (t1/2) 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 [14C]-dapagliflozin dose, 96% was recovered, 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose was excreted as parent drug.
Linearity: Dapagliflozin exposure increased proportional to the increment in dapagliflozin dose over the range of 0.1 to 500 mg and its pharmacokinetics did not change with time upon repeated daily dosing for up to 24 weeks.

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 and 85, 52,18 and 11 g of glucose/day was excreted by subjects with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. 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 (a 65 years): There is no clinically meaningful increase in exposure based on age alone in subjects up to 70 years old. However, an increased exposure due to age-related decrease in renal function can be expected. There are insufficient data to draw conclusions regarding exposure in patients >70 years old.
Gender: The mean dapagliflozin AUCs 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 have not been studied.
Metformin:
Absorption: After an oral dose of metformin, tmax is reached in 2.5 h. Absolute bioavailability of a 500 mg or 850 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces 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 1µg/mL.
Biotransformation: Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.
Elimination: Renal clearance of metformin is > 400 mUmin, 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.

THERAPEUTIC INDICATIONS:
XIGA Met is indicated in adults aged 78 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control:
- In patients inadequately controlled on their maximally tolerated dose of metformin alone
- In combination with other glucose-lowering medicinal products, including insulin,
- In patients inadequately controlled with metformin and medicinal products
- In patients already being treated with the combination of dapagliflozin and metformin as separate tablets

POSOLOGY & METHOD OF ADMINISTRATION:
Posology: Adults with normal renal function (glomerular filtration rate (GFR) a 90 mL/min): For patients inadequately controlled on metformin monotherapy or metformin in combination with other glucose-lowering medicinal products including insulin The recommended dose is one tablet twice daily. Each tablet contains a fixed dose of dapagliflozin and metformin. Patients not adequately controlled on metformin alone or in combination with other glucose-lowering medicinal products, including insulin, should receive a total daily dose of XIGA Met equivalent to dapagliflozin 10 mg, plus the total daily dose of metformin, or the nearest therapeutically appropriate dose, already being taken. When XIGA Met 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 hypoglycaemia. For patients switching from separate tablets of dapagliflozin and ***Metformin:*** Patients switching from separate tablets of dapagliflozin (10 mg total daily dose) and metformin to XIGA Met 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 containing medicinal 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. 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 initiation of metformin in patients with GFR < 60 mUmin. If no adequate strength of XIGA Met is available, individual mono-components should be used instead of the fixed dose combination.
Hepatic impairment: This medicinal product must not be used in patients with hepatic impairment.
Elderly (b 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. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in elderly patients. Risk of volume depletion with dapagliflozin should also be taken into account. Due to the limited therapeutic experience with dapagliflozin in patients 75 years and older, initiation of therapy in this population is not recommended.
Pediatric population: The safety and efficacy of XIGA Met in children and adolescents aged 0 to < 18 years have not yet been established. No data are available. Method of administration should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin.

CONTRAINDICATIONS:
XIGA Met is contraindicated in patients with:
- 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 (GER< 30 mUmin); -
- Acute conditions with the potential to alter renal function such as:
- Dehydration,
- Severe infection,
- Shock;
- Acute or chronic disease which may cause tissue hypoxia such as:
- Cardiac or respiratory failure,
- Recent myocardial infarction,
- Shock;
- Hepatic impairment
- Acute alcohol intoxication,
- Alcoholism

SPECIAL WARNING & PRECAUTIONS:
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), XIGA Met 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 nonsteroidal anti-inflammatory drugs INSAIDs]) 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 characterized by acidotic dyspnea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking XIGA Met 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 glycaemic 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. XIGA Met 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. For renal function with GFR levels < 60 mUmin 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 mUmin, treatment should be discontinued. Metformin is contraindicated in patients with GFR of < 30 mUmin 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, hypotension and/or electrolyte imbalances. Due to its mechanism of action, dapagliflozin increases diuresis associated with a modest decrease in blood pressure, which may be more pronounced in patients with high blood glucose concentrations. This medicinal product is not recommended for use in patients receiving loop diuretics or who are volume depleted, e.g. due to acute illness (such as gastrointestinal illness). Caution should be exercised in patients for whom a dapagliflozin-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 elderly patients. For patients receiving this medicinal product, in case of intercurrent conditions that may lead to volume depletion, 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: Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors, including dapagliflozin. 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 dapagliflozin. 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 dapagliflozin should be discontinued immediately. Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. In both cases, treatment with dapagliflozin may be restarted once the patient's condition has stabilised. 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

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clear precipitating factor is identified and resolved. The safety and efficacy of dapagliflozin in patients with type 1 diabetes have not been established and dapagliflozin should not be used for treatment of patients with type 1 diabetes. Limited data from clinical trials suggest that DKA occurs with common frequency when patients with type 1 diabetes are treated with SGLT2 inhibitors. Post-marketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment. Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perinea! area, with fever or malaise. Be aware that either uro-genital infection or perinea! abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, XIGA Met should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.
Urinary tract infections: Urinary tract infections were more frequently reported for dapagliflozin compared to placebo in a pooled analysis up to 24 weeks. Pyelonephritis was uncommon and occurred at a similar frequency to control. 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 (a 65 years): Elderly patients 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 such as angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to elderly patients as to all patients. In subjects > 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to renal impairment or failure compared with placebo. The most commonly reported adverse reaction related to renal function was serum creatinine increases, the majority of which were transient and reversibl. Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics. In subjects > 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to volume depletion. Therapeutic experience in patients 75 years and older is limited. Initiation of therapy in this population is not recommended.
Cardiac failure: Experience in NYHA class I-II is limited, and there is no experience in clinical studies with dapagliflozin in NYHA class III-IV. While a causal relationship between dapagliflozin and bladder cancer is unlikely, as a precautionary measure, this medicinal product is not recommended for use in patients concomitantly treated with pioglitazone. Available epidemiological data for pioglitazone suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone. increase was observed with dapagliflozin treatment, therefore, caution in patients with already elevated haematocrit is warranted. An increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term, clinical studies with another SG LT2 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. 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. XIGA Met 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: XIGA Met must be discontinued at the time of surgery with 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. Change in clinical status of patients with previously controlled type 2 diabetes as this medicinal product contains metformin, a patient with type 2 diabetes previously well-controlled on it who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, treatment must be stopped immediately and other appropriate corrective measures initiated.

INTERACTIONS WITH MEDICINAL PRODUCTS &OTHER FORM OF INTERACTIONS:
Co-administration 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 XIGA Met. 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 CYP1 A2, CYP2B6 or CYP3A4. Therefore, this medicinal product is not expected to alter the metabolic clearance of co-administered medicinal products that are metabolised 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 co-administration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolising 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 co-administration 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: 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 Cmax 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 co-administered.
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.
Iodinated Contrast Agents: XIGA Met 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 perfomed, 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: 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.

FERTILITY, PREGNANCY AND LACTATION:
Pregnancy: There are no data from the use of XIGA Met or dapagliflozin in pregnant women. A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital malformations.
Nursing Mothers: 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.
Effects on ability to drive and use machines: XIGA Met has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when this medicinal product is used in combination with other glucose lowering medicinal products known to cause hypoglycaemia

ADVERSE REACTIONS:
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice. The adverse reactions identified from up to 24-week (short-term) data regardless of glycaemic rescue, except those marked with, for which adverse reaction and frequency categories are based on information from the metformin Summary of Product Characteristics available in the European Union.
Vulvovaginitis, balanitis and related genital infections: Includes, the 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.
Urinary tract infection: Includes the urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis.
Volume depletion: Includes dehydration, hypovolaemia, hypotension.
Polyuria: Includes pollakiuria, polyuria, urine output increased.
B_{12} Deficiency: Long-term treatment with metformin has been associated with a decrease in vitamin B_{12} absorption which may very rarely result in clinically significant vitamin B_{12} deficiency (e.g. megaloblastic anaemia).
Gastrointestinal symptoms: Such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.
Hypersensitivity: Adverse reaction was identified through post-marketing surveillance with the use of dapagliflozin include rash generalised, rash pruritic, rash macular, rash maculo-popular, rash pustular, rash vesicular, and rash erythematous.
Increased creatinine: Adverse reactions related to increased creatinine were grouped (e.g. include decreased renal creatinine clearance, renal impairment, increased blood creatinine and decreased glomerular filtration rate). Further evaluation of patients who had renal-related adverse events showed that most had serum creatinine changes of 0.5 mg/dL from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.
Parathyroid hormone (PTH): Small increases in serum PTH levels were observed with increases being larger in subjects with higher baseline PTH concentrations. Bone mineral density measurements in patients with normal or mildly impaired renal function did not indicate bone loss over a treatment period of two years.

OVERDOSAGE:
Removal of dapagliflozin by haemodialysis has not been studied. The most effective method to remove metformin and lactate is haemodialysis. Dapagliflozin did not show any toxicity in healthy subjects at single oral doses up to 500 mg (50 times the maximum recommended human dose). These subjects had detectable glucose in the urine fora dose-related period of time (at least 5 days for the 500 mg dose), with no reports of dehydration, hypotension or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycaemia was similar to placebo. In clinical studies where once daily doses of up to 100 mg (10 times the maximum recommended human dose) were administered for 2 weeks in healthy subjects and type 2 diabetes subjects, the incidence of hypoglycaemia was slightly higher than placebo and was not dose-related. Rates of adverse events including dehydration or hypotension were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters, including serum electrolytes and biomarkers of renal function. 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 hospital.

INSTRUCTIONS:
- Store below 30°C.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:
XIGA Met 5/850 Tablet : Pack of 2 x 7 tablets.
XIGA Met 5/1000 Tablet : Pack of 2 x 7 tablets.

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATION PLEASE CONTACT:

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