XIGA™
[DAPAGLIFLOZIN]
Tablet

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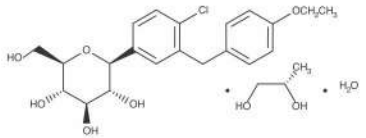
COMPOSITION:
XIGA Tablet 5 mg:
Each film coated tablet contains:
Dapagliflozin propanediol monohydrate equivalent to
Dapagliflozin ..... 5 mg.

Product Specs.: BP

XIGA Tablet 10 mg:
Each film coated tablet contains:
Dapagliflozin propanediol monohydrate equivalent to
Dapagliflozin ..... 10 mg.

Product Specs.: BP

DESCRIPTION:
Dapagliflozin is described chemically as D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4 ethoxyphenyl) methyl]phenyl]-, (1S)-, compounded with (2S)-1,2-propanediol, hydrate (1:1:1). The empirical formula is $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$ and the molecular weight is 502.98.
The structural formula is:



CLINICAL PHARMACOLOGY:
Mechanism of Action:
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.
Pharmacokinetics:
Absorption: 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.
Distribution: Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with renal or hepatic impairment.
Metabolism: 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 [14C]-dapagliflozin dose and is the predominant drug-related component in human plasma.
Elimination: Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [14C]-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 ($t_{½}$) for dapagliflozin is approximately 12.9 hours following a single oral dose of 10 mg.
Pharmacokinetics in special populations:
Renal Impairment: 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, then patients with type 2 diabetes with normal renal function. The impact of hemodialysis on dapagliflozin exposure is not known.
Hepatic Impairment: 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 control.
Effects of Age, Gender, Race, and Body Weight on Pharmacokinetics: Based on a population pharmacokinetic analysis, age, gender, race, and body weight do not have a clinically meaningful effect on the pharmacokinetics of dapagliflozin and thus, no dose adjustment is recommended.
Pediatric: Pharmacokinetics in the pediatric population is not known.

INDICATIONS AND USAGE:
XIGA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Limitation of use:
XIGA is not recommended for patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

DOSAGE AND ADMINISTRATION:
Administration: The recommended starting dose of XIGA is 5 mg once daily, taken in the morning, with or without food. In patients tolerating XIGA 5 mg once daily who require additional glycemic control, the dose can be increased to 10 mg once daily. In patients with volume depletion, correcting this condition prior to initiation of XIGA is recommended.

DOSE MODIFICATION RECOMMENDATIONS:
Patients with Renal Impairment:
- Assessment of renal function is recommended prior to initiation of XIGA therapy and periodically thereafter.
- XIGA should not be initiated in patients with an eGFR less than 60 mL/min/1.73 m^2.
- No dose adjustment is needed in patients with mild renal impairment (eGFR of 60 mL/min/1.73 m^2 or greater).
- XIGA should be discontinued when eGFR is persistently less than 60 mL/min/1.73 m^2.

CONTRAINDICATIONS:
- History of a serious hypersensitivity reaction to XIGA.
- Severe renal impairment, end-stage renal disease (ESRD), or patients on dialysis.

WARNINGS AND PRECAUTIONS:
Hypotension: XIGA causes intravascular volume contraction. Symptomatic hypotension can occur after initiating XIGA 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 XIGA in patients, volume status should be assessed and corrected. Monitor for signs and symptoms of hypotension after initiating therapy.
Impairment in renal function: XIGA 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 XIGA. Renal function should be evaluated prior to initiation of XIGA and monitored periodically thereafter.
Hypoglycemia with concomitant use with insulin and insulin secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. XIGA can increase the risk of hypoglycemia when combined with insulin 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 XIGA.
Genital mycotic infections: XIGA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections.
Increases in low-density lipoprotein cholesterol (ldl-c): Increases in LDL-C occur with XIGA. Monitor LDL-C and treat per standard of care after initiating XIGA.
Bladder cancer: XIGA should not be used in patients with active bladder cancer. In patients with prior history of bladder cancer, the benefits of glycemic control versus unknown risks for cancer recurrence with XIGA should be considered.
Macrovascular outcomes: Conclusive evidences of macrovascular risk reduction with XIGA or any other antidiabetic drug are insufficient.

DRUG INTERACTIONS:
Positive urine glucose test: Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.
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 alternative methods to monitor glycemic control.

USE IN SPECIFIC POPULATION:
Pregnancy:
Pregnancy Category C:
During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. XIGA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers: It is not known whether XIGA is excreted in human milk, but because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from XIGA, a decision should be made whether to discontinue nursing or to discontinue XIGA, taking into account the importance of the drug to the mother.
Pediatric use: Safety and effectiveness of Dapagliflozin in pediatric patients under 18 years of age have not been established.
Renal impairment: Based on its mechanism of action, XIGA is not expected to be effective in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) or ESRD.
Hepatic Impairment: The benefit-risk for the use of dapagliflozin in patients with severe hepatic impairment should be individually assessed since the safety and efficacy of dapagliflozin have not been known in this population.

ADVERSE REACTIONS:
Specific: Hypotension, Impairment in Renal Function, Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues, Genital Mycotic Infections, Increases in Low-Density Lipoprotein Cholesterol (LDL-C), Bladder Cancer.
Allergic reaction: Hypersensitivity reactions (e.g., angioedema, urticaria, hypersensitivity) serious anaphylactic reactions and severe cutaneous adverse reactions and angioedema were reported at 0.2% Dapagliflozin-treated patients. If hypersensitivity reactions occur, discontinue use of XIGA; treat per standard of care and monitor until signs and symptoms resolve.
Laboratory tests: Increase in Hematocrit, Increase in Serum Inorganic Phosphorus, Increase in Low-Density Lipoprotein Cholesterol.

OVERDOSAGE: 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.

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

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

PRESENTATION:

XIGA Tablet 5 mg	:	Pack of 2 x 7 tablets.
XIGA Tablet 10 mg	:	Pack of 2 x 7 tablets.

FOR FURTHER INFORMATION PLEASE CONTACT:

CCL
Manufactured by:
CCL Pharmaceuticals (Pvt.) Ltd.
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