BIOS LAB PVT. LTD.

8, MILAN COMPLEX, SARKHEJ, AHMEDABAD.

QUALITY CONTROL DEPARTMENT

CERTIFICATE OF ANALYSIS

See Rule 150 E (F) Under The Drugs & Cosmetic Act 1940 and The Rules there under

Report No. : **F/T/20832** **Mfg. No.:** **6/UA/2019, 5/UA/SC/P-2019**

Sample Name : **BIOXIGA™ - 10 TABLETS**

Generic Name : **Dapagliflozin 10 mg Tablets**

Product Name	**BIOXIGA™ - 10**	**A.R.No.**	F/T/20832	**Ref. No.**	RM2512
Batch No.	199AB01	**Batch Size**	0.50 Lacs Tablets		
Mfg. Date	FEB. 2021	**Sample Qty.**	40 Tablets		
Exp. Date	JAN. 2023	**Test as per**	Manufacturer Specification		
Date of Receipt	04-03-2021	**Date of Release**	17-03-2021		

S NO.	TEST	SPECIFICATION	RESULT
1.	Description	Yellow coloured, round shape, biconvex with plane faces, film coated tablet	Yellow coloured, round shape, biconvex with plane faces, film coated tablet
2.	Identification	Positive test of assay	Complies
3.	Average weight	142 mg ± 7.5%	143.09 mg
4.	Uniformity of weight	± 7.5% of average weight	Upper Limit +1.96% Lower Limit -4.32%
5.	Uniformity of content	NLT 85.0% - NMT 115.0%	102.34%, 101.32%, 96.59%, 97.61%, 95.57% 99.59%, 100.23%, 98.69%, 92.55%, 97.16%
6.	Disintegration time	NMT 30 minutes	04 minutes 15 seconds
7.	ASSAY	Each film coated tablet contains:	
	Dapagliflozin propanediol monohydrate Eq. to Dapagliflozin - 10 mg	NLT 90.0% - NMT 110.0%	9.98 mg (99.81%)

Reports: The sample reffered to above is of standard quality as defined in the act and the Rules made there under

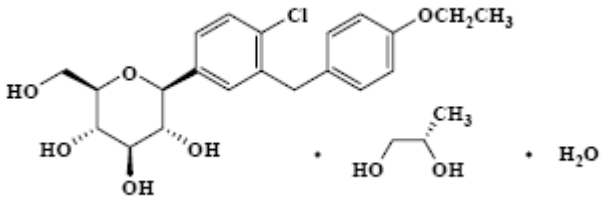
Conclusion: The above collected sample is complies as per I.H Specification.

*** Manufactured by:** SARV PHARMACEUTICALS (HARIDWAR)

BIOXIGA™- 10

PRODUCT DESCRIPTION
Each film coated tablet contains
Dapagliflozin propanediol monohydrate
Eq. to Dapagliflozin - 10 mg
Excipients - q.s

DESCRIPTION
Dapagliflozin:
Structural formula:



Molecular formula: $C_{21}H_{25}ClO_6 \bullet C_3H_8O_2 \bullet H_2O$

Chemical name: D-glucitol, 1, 5-anhydro-1-*C*-[4-chloro-3-[(4-ethoxyphenyl) methyl] phenyl]-, (1*S*)-, compd. with (2*S*)-1, 2-propanediol, hydrate (1:1:1)

Molecular weight: 502.98 g/mol; 408.87 g/mol (dapagliflozin)

pKa: 12.6 (estimated)

Dapagliflozin is a sodium-glucose cotransporter 2 inhibitor indicated for managing diabetes mellitus type 2. When combined with diet and exercise in adults, dapagliflozin helps to improve glycemic control by inhibiting glucose resorption in the proximal tubule of the nephron and causing glycosuria.

PHARMACOLOGIC PROPERTIES:
MECHANISM OF ACTION

Dapagliflozin is a reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2) that improves glycemic control in patients with type 2 diabetes mellitus by reducing renal glucose reabsorption leading to urinary excretion of excess glucose (glucuresis).

SGLT2 is selectively expressed in the kidney. SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary excretion of excess glucose. 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. Dapagliflozin acts independently of insulin secretion and insulin action.

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 greater than 1400 times more selective for SGLT2 vs. SGLT1, the major transporter in the gut responsible for glucose absorption.

PHARMACODYNAMICS

Increases in the amount of glucose excreted in the urine were observed in patients 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 patients with type 2 diabetes mellitus for 12 weeks. This glucose elimination rate approached the maximum glucose excretion observed at 20 mg/day of dapagliflozin. Evidence of sustained glucose excretion was seen in patients 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. Urinary volume increases in patients with type 2 diabetes mellitus treated with BIOXIGA 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 reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from 18.3 to 48.3 μmol/L (0.33 mg/dL to 0.87 mg/dL).

PHARMACOKINETICS

Absorption

Dapagliflozin was rapidly and well absorbed after oral administration and can be administered with or without food. Geometric mean steady-state dapagliflozin C_{max} and AUC_{τ} values following once daily 10 mg doses of dapagliflozin were 158 ng/mL and 628 ng/mL, respectively. Maximum dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. The C_{max} and AUC values increased proportionally to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Food had relatively modest effects on the pharmacokinetics of dapagliflozin in healthy patients. Administration with a high-fat meal decreased dapagliflozin C_{max} by up to 50% and prolonged T_{max} by approximately 1 hour, but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful.

Distribution

Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g. renal or hepatic impairment).

Metabolism

Dapagliflozin is a C-linked glucoside, meaning the aglycone component is attached to glucose by a carbon-carbon bond, thereby conferring stability against glucosidase

enzymes. The mean plasma terminal half-life ($t_{1/2}$) for dapagliflozin was 12.9 hours following a single oral dose of BIOXIGA 10 mg to healthy patient. 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 was the predominant drug-related component in human plasma, accounting for 42% (based on AUC $_{[0\text{-}12\ h]}$) of total plasma radioactivity, similar to the 39% contribution by parent drug. Based on AUC, no other metabolite accounted for >5% of the total plasma radioactivity at any time point measured. 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.

Excretion

Dapagliflozin and related metabolites are primarily eliminated via urinary excretion, of which less than 2% is unchanged dapagliflozin. After administration of 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

Pediatrics (<18 years of age): Safety and effectiveness of BIOXIGA in pediatric and adolescent population have not been established, therefore BIOXIGA should not be used in this population.

Geriatrics (≥65 years of age): After controlling for renal function (eGFR), there was no conclusive evidence suggesting that age is an independent factor affecting efficacy. In patients ≥65 years of age, a higher proportion of patients treated with BIOXIGA had adverse events related to volume depletion and renal impairment or failure compared with placebo. The most commonly reported adverse events related to renal impairment or failure in patients ≥65 years of age in any treatment group were creatinine renal clearance decreased, renal impairment, and increased blood creatinine. Older patients are more likely to have impaired renal function (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Renal Function, and ADVERSE REACTIONS).

Age: No dosage adjustment for dapagliflozin is recommended on the basis of age. The mean dapagliflozin systemic exposure (AUC) in young patients was lower than in the reference group and 25% higher in elderly patients compared to the reference group. These differences in systemic exposure were considered not to be clinically meaningful.

Gender: No dosage adjustment is recommended for dapagliflozin on the basis of gender. The mean dapagliflozin AUC_{ss} in females was estimated to be 22% higher than in males.

Race: No dosage adjustment is recommended on the basis of race (white, black or Asian). Differences in systemic exposures between these races were small. Compared to whites, Asian had no difference in estimated mean dapagliflozin systemic exposures. Compared to whites, black had lower estimated mean dapagliflozin systemic exposures.

Body weight: No dose adjustment is recommended on the basis of weight. No dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with high body weight (≥120 kg) and low body weight (<50 kg) is recommended.

Renal impairment: BIOXIGA (dapagliflozin) is contraindicated in patients with moderate to severe renal impairment (eGFR <60 mL/min/1.73m^2). BIOXIGA should be discontinued when eGFR is <60 mL/min/1.73m^2 (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION). At steady-state (20 mg once-daily dapagliflozin for 7 days), patients with type 2 diabetes and mild, moderate or severe renal impairment (as determined by iohexol clearance) had mean systemic exposures of dapagliflozin that were higher, than those of patients with type 2 diabetes and normal renal function. Higher systemic exposures to dapagliflozin in patients with type 2 diabetes mellitus and renal impairment did not result in a correspondingly higher renal glucose clearance or total cumulative glucose excretion. The renal glucose clearance and 24-hour glucose excretion were lower in patients with moderate or severe renal impairment as compared to patients with normal and mild renal impairment. 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 patients with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. There were no differences in the protein binding of dapagliflozin between renal impairment groups or compared to healthy patient. The impact of hemodialysis on dapagliflozin exposure is not known.

Hepatic impairment: A single dose (10 mg) dapagliflozin clinical pharmacological analysis was conducted in patients with mild, moderate or severe hepatic impairment and healthy matched controls. There were no differences in the protein binding of dapagliflozin between patients with hepatic impairment compared to healthy patients. In patients with mild or moderate hepatic impairment mean C_{max} and AUC of dapagliflozin were up to 12% and 36% higher. No dose adjustment from the proposed usual dose of dapagliflozin is proposed for these populations. In patients with severe hepatic impairment (Child-Pugh class C) mean C_{max} and AUC of dapagliflozin were up to 40% and 67% higher than matched healthy controls, respectively.

Pregnant Women: BIOXIGA must not be used in pregnancy. In the time period corresponding to second and third trimesters of pregnancy with respect to human renal maturation, maternal exposure to dapagliflozin was associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny (see TOXICOLOGY). There are no adequate and well-controlled studies of BIOXIGA in pregnant women. When pregnancy is detected, BIOXIGA should be discontinued.
Use in Pregnancy: Category D

Nursing Women: BIOXIGA must not be used by a nursing woman. BIOXIGA must be avoided during the first 2 years of life (see TOXICOLOGY). It is not known whether BIOXIGA and/or its metabolite are excreted in human milk.

Monitoring and Laboratory Tests

Blood glucose and HbA1c: Response to BIOXIGA treatment should be monitored by periodic measurements of blood glucose and HbA1c levels. Due to its mechanism of action, patients taking BIOXIGA will test positive for glucose in their urine (see DRUG INTERACTIONS, Drug-Laboratory Interactions).

Renal function: Renal function should be assessed prior to initiation of BIOXIGA and regularly thereafter. BIOXIGA is contraindicated in patients with an eGFR <60 mL/min/1.73m^2 (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION). Monitoring of renal function is recommended prior to and following initiation of any concomitant drug which might have an impact on renal function.

Reduced intravascular volume: BIOXIGA is not recommended for use in patients who are volume depleted (see DOSAGE AND ADMINISTRATION). Before initiating BIOXIGA, assess volume status, particularly in patients at risk (see WARNINGS AND PRECAUTIONS, Cardiovascular, and DOSAGE AND ADMINISTRATION) as well as in case of intercurrent conditions that may lead to fluid loss (such as a gastrointestinal illness) for patients already taking BIOXIGA. In these patients, careful monitoring of volume status (e.g., physical examination, blood pressure measurements, laboratory tests, including hematocrit, serum electrolytes and renal function tests) is recommended. Temporary interruption of treatment with BIOXIGA should be considered until fluid loss is corrected.

LDL-cholesterol: LDL-C levels should be measured at baseline and at regular intervals during treatment with BIOXIGA due to dose-dependent increases in LDL-C seen with therapy.

INDICATIONS

Monotherapy: BIOXIGA (dapagliflozin) is indicated for use as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance.

Add-on combination: BIOXIGA is indicated in adult patients with type 2 diabetes mellitus to improve glycemic control in combination with

- metformin,
- a sulfonylurea,
- metformin and a sulfonylurea,
- sitagliptin (alone or with metformin),
- insulin (alone or with metformin),

When metformin alone or the existing therapy listed above, along with diet and exercise, do not provide adequate glycemic control.

Geriatrics (≥65 years of age): BIOXIGA should be used with caution in this population as a higher proportion of patients ≥65 years of age treated with BIOXIGA had adverse reactions related to volume depletion and renal impairment or failure, compared to patients treated with placebo (see WARNINGS AND PRECAUTIONS, DOSAGE AND

ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Pediatrics (<18 years of age): BIOXIGA should not be used in pediatric patients. Safety and effectiveness of BIOXIGA have not been established in patients under 18 years of age.

Important Limitations of Use: BIOXIGA is not indicated for use in combination with pioglitazone (see WARNINGS AND PRECAUTIONS).

CONTRAINDICATIONS

BIOXIGA (dapagliflozin) is contraindicated in:

- Patients with a history of hypersensitivity reaction to the active substance or to any of the excipients. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.
- Patients with moderate to severe renal impairment, defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2, end-stage renal disease [ESRD] and patients on dialysis.

WARNINGS & PRECAUTIONS

Serious Warnings and Precautions

Diabetic Ketoacidosis

- Diabetic ketoacidosis (DKA), a serious life- threatening condition requiring urgent hospitalization, have been reported in patients with type 2 diabetes mellitus (T2DM) treated with BIOXIGA (dapagliflozin) and other sodium-glucose co-transporter 2 (SGLT2) inhibitors. A number of these cases have been atypical with blood glucose values below 13.9 mmol/L (250 mg/dL) (see ADVERSE REACTIONS). Some cases of DKA have been fatal.
- Patients should be assessed for diabetic ketoacidosis immediately if non-specific symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, anorexia, excessive thirst and unusual fatigue or sleepiness occur, regardless of blood glucose level. If DKA is suspected or diagnosed, BIOXIGA should be **discontinued immediately**.
- BIOXIGA should not be used for the treatment of DKA or in patients with a history of DKA.
- BIOXIGA is not indicated, and should not be used, in patients with type 1 diabetes.

CARCINOGENESIS AND MUTAGENESIS

Bladder cancer: There are insufficient data to determine whether BIOXIGA has an effect on pre-existing bladder tumors (see ADVERSE REACTIONS). Consequently, BIOXIGA should not be used in patients with active bladder cancer and should be used with caution in patients with a prior history of bladder cancer.

Use in patients treated with pioglitazone: The relationship between dapagliflozin, pioglitazone and bladder cancer is uncertain. Therefore, as a precautionary measure, dapagliflozin is not indicated for use in patients concomitantly treated with pioglitazone.

CARDIOVASCULAR

Use in patients at risk for volume depletion, hypotension and/or electrolyte imbalances: Due to its mechanism of action, dapagliflozin causes diuresis that may be associated with decreases in blood pressure, which may be more pronounced in patients with high blood glucose concentrations.

Dapagliflozin is not recommended for use in patients who are volume depleted. Patients most susceptible to adverse reactions related to reduced intravascular volume (e.g., postural dizziness, orthostatic hypotension, hypotension or renal failure) include patients with renal impairment, patients with known cardiovascular disease, patients on antihypertensive therapy (particularly on loop diuretics or medications that interfere with the renin-angiotensin- aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs])), elderly patients, patients with low systolic blood pressure, or in case of intercurrent conditions that may lead to volume depletion (such as gastrointestinal illness) (see ADVERSE REACTIONS, DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION). Careful monitoring of volume status is recommended. Temporary interruption of BIOXIGA should be considered for patients who develop volume depletion until the depletion is corrected (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, and ADVERSE REACTIONS).

Endocrine and Metabolism

Diabetic ketoacidosis: A serious life-threatening condition requiring urgent hospitalization, have been reported in patients with type 2 diabetes mellitus treated with BIOXIGA and other SGLT2 inhibitors. In a number of reported cases, the presentation of the condition was atypical with only moderately increased blood glucose values below 13.9 mmol/L (250 mg/dL) (see ADVERSE REACTIONS). Some cases of DKA have been fatal.

BIOXIGA is not indicated, and should not be used, in patients with type 1 diabetes. The diagnosis of T2DM should therefore be confirmed before initiating BIOXIGA.

DKA must be considered in the event of non-specific symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, anorexia, excessive thirst, and unusual fatigue or sleepiness. If DKA is suspected, regardless of blood glucose level, patients should discontinue BIOXIGA treatment and be assessed for DKA immediately.

Interruption of treatment with BIOXIGA should be considered in T2DM patients who are hospitalized for major surgical procedures, serious infections or acute serious medical illness. Conditions that can precipitate DKA while taking BIOXIGA include a very low carbohydrate diet (as the combination may further increase ketone body production), dehydration, high alcohol consumption and a low beta-cell function reserve. These patients should be monitored closely. Caution should also be taken when reducing the insulin dose in patients requiring insulin (see DOSAGE AND ADMINISTRATION).

Use with medications known to cause hypoglycemia: Insulin and insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with BIOXIGA (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

Increases in Low-Density Lipoprotein (LDL-C): Dose-related increases in LDL-C are seen with BIOXIGA treatment (see ADVERSE REACTIONS). LDL-C levels should be monitored.

Genitourinary

Genital mycotic infections: Patients, particularly those with a history of genital mycotic infections, should be advised that BIOXIGA increases the risk of genital mycotic infections (see ADVERSE REACTIONS).

Urinary tract infections (including urosepsis and pyelonephritis): Treatment with BIOXIGA increases the risk for urinary tract infections (see ADVERSE REACTIONS). There have been post-marketing reports of serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization in patients treated with BIOXIGA.

Hematologic

Elevated hemoglobin and hematocrit: Mean hemoglobin and hematocrit increased in patients administered BIOXIGA, as did the number of patients with abnormally elevated values for hemoglobin/hematocrit (see ADVERSE REACTIONS). BIOXIGA should be used with caution in patients with an elevated hematocrit.

Hepatic/Biliary/Pancreatic

Elevations in hepatic transaminases have been reported in dapagliflozin treated patients, however a causal relationship with dapagliflozin has not been established. BIOXIGA exposure is increased in patients with severe hepatic impairment (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY). Use of BIOXIGA is not recommended in patients with severe hepatic impairment.

Renal

BIOXIGA increases serum creatinine and decreases eGFR in a dose dependent fashion. Renal function abnormalities have occurred after initiating BIOXIGA.

Post-marketing cases of acute kidney injury, including acute renal failure, shortly after the initiation of BIOXIGA treatment have been reported (see WARNINGS AND PRECAUTIONS, Cardiovascular and ADVERSE REACTIONS). Patients with hypovolemia may be more susceptible to these changes (see ADVERSE REACTIONS).

Renal function should be assessed prior to initiation of BIOXIGA and regularly thereafter. BIOXIGA should be discontinued when eGFR is <60 mL/min/1.73m^2 (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

The efficacy of BIOXIGA is dependent on renal function. BIOXIGA is contraindicated in patients with moderate to severe renal impairment (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2) or end-stage renal disease [ESRD]. In such patients BIOXIGA did not improve glycemic control, and adverse reactions were more frequent (see ADVERSE REACTIONS).

ADVERSE EFFECTS

The most commonly reported adverse events during treatment with BIOXIGA 10 mg

(≥5%) were female genital mycotic infections, nasopharyngitis and urinary tract infections. The most commonly reported events leading to discontinuation and reported in BIOXIGA 10 mg-treated patients were renal impairment, decrease in creatinine clearance, increased blood creatinine, urinary tract infections, and vulvovaginal mycotic infection.
A total serious adverse drug events, from patients taking Dapagliflozin 5 mg daily (change of bowel habit, hypoglycemia), from patients taking BIOXIGA 10 mg daily (constipation, rotator cuff syndrome).

Description of Selected Adverse Reactions

Volume depletion and hypotension: Events related to volume depletion (including reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension) were reported in patients who received Dapagliflozin 5 mg and BIOXIGA 10 mg. A nalyses of patients on loop diuretics or ≥65 years of age of patients with events related to volume depletion were higher in patients treated with BIOXIGA 10 mg than in those treated with placebo (events in patients on loop diuretics: 2.5% vs. 1.5%; events in patients ≥65 years of age: 1.7% vs. 0.8%, respectively). Patients with type 2 diabetes and hypertension, postural blood pressure measurement revealed orthostatic hypotension in 3.2% of BIOXIGA 10 mg-treated patients.

Genital mycotic infections: Events of genital mycotic infections were reported in patients who received, BIOXIGA 10 mg Infections were more frequently reported in females than in males. The most frequently reported genital infections were vulvovaginal mycotic infections in females, and balanitis in males.
Patients who had a previous history of recurrent genital mycotic infections, were more likely to have an event of genital infection,

Urinary tract infections: Events of urinary tract infections were reported in patients who received BIOXIGA 10 mg. Infections were more frequently reported in females than in males.

Hypoglycemia: The frequency of hypoglycemia depended on the type of background therapy. BIOXIGA as an add-on to sulfonylurea or as an add-on to insulin therapy had higher rates of hypoglycemia with BIOXIGA treatment than with placebo treatment (see WARNINGS AND PRECAUTIONS).

***Monotherapy and add-on to metformi*n:** BIOXIGA used as monotherapy, add-on to metformin, and initial combination with metformin, there were no major episodes of hypoglycemia reported. The frequency of minor episodes of hypoglycemia reported.

Add-on to sulfonylureas: BIOXIGA added on to glimepiride, there was one episode of major hypoglycemia reported in a patient treated with dapagliflozin 2.5 mg plus glimepiride. Minor episodes of hypoglycemia were reported in patients treated with BIOXIGA 10 mg plus glimepiride.

Add-on to metformin and to a sulfonylurea: In the add-on to combination with metformin and a sulfonylurea, there were no episodes of major hypoglycemia reported. Minor episodes of hypoglycemia were reported patients treated with BIOXIGA 10 mg plus metformin and a sulfonylurea.

Add-on to sitagliptin alone or with metformin: BIOXIGA 10 mg added on to sitagliptin (with or without metformin), one major episode of hypoglycemia was reported in a patient treated with BIOXIGA 10 mg plus sitagliptin (without metformin). Minor episodes of hypoglycemia were reported in patients treated with BIOXIGA 10 mg or placebo added on to sitagliptin (with or without metformin).

Add-on to insulin: Major episodes of hypoglycemia were reported in patients treated with BIOXIGA 10 mg or placebo added on to insulin. Minor episodes were reported in patients treated with BIOXIGA 10 mg or placebo added on to insulin,

Bladder cancer: Newly diagnosed cases of bladder cancer were reported in very least cases when treated with BIOXIGA. Bladder cancer risk factors (e.g., smoking, age) and hematuria (a potential indicator of pre-existing tumors) were balanced between treatment arms at baseline. There were too few cases to determine whether the emergence of these events is related to BIOXIGA.

Cardiovascular safety: Cardiovascular events were adjudicated by an independent adjudication. The primary endpoint was the time to first event of the following outcomes: cardiovascular death, stroke, myocardial infarction, and hospitalization for unstable angina. There was no evidence of an increase in the primary endpoint with BIOXIGA 10 mg.

Patients with renal impairment: Safety was also assessed in diabetic patients with moderate renal impairment (eGFR 30 to 60 mL/min/1.73m^2). With BIOXIGA 10 mg, these eGFR reductions and greater increases in mean PTH and serum phosphorus BIOXIGA 10 mg. Overall, adverse event of bone fracture reported in least cases of BIOXIGA 10 mg.

Diabetic ketoacidosis: Cases of DKA, a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with type 2 diabetes treated with BIOXIGA and other SGLT2 inhibitors. Some cases of DKA have been fatal. BIOXIGA is not indicated, and should not be used, in patients with type 1 diabetes. In some cases, the presentation of the condition was atypical, with blood glucose values only moderately elevated (<13.9 mmol/L (250 mg/dL) (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

Abnormal Hematologic and Clinical Chemistry Findings

Increases in serum creatinine, blood urea nitrogen (BUN) and decreased eGFR: In BIOXIGA-treated patients, mean eGFR decreased by Week 1 and then increased toward eGFR baseline values over time to Week 24.

Changes from baseline in serum creatinine were consistent with changes in eGFR. Mean serum creatinine levels increased at Week 1 and decreased toward baseline at Week 24. There were small increases in BUN. Mean BUN levels increased at Week 1 and values remained stable through Weeks 24 and 102.

Post-Marketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Genitourinary: severe urinary tract infections; urosepsis and pyelonephritis

Metabolism: diabetic ketoacidosis

Renal and urinary disorders: acute kidney injury, including acute renal failure

Skin and subcutaneous tissue disorders: rash (including rash generalized, rash pruritic, rash macular, rash macular-papular, rash pustular and rash vesicular)

DRUG INTERACTION

The metabolism of dapagliflozin is primarily mediated by UGT1A9-dependent glucuronide conjugation. The major metabolite, dapagliflozin 3-O-glucuronide, is not an SGLT2 inhibitor.

Pharmacokinetic interactions

Effect of other drugs on dapagliflozin: The pharmacokinetics of dapagliflozin were not altered by the coadministered drugs.

- Dapagliflozin was not markedly affected by rifampin co-administration (45 g).
- Pioglitazone is not indicated for co-administration with dapagliflozin.

Effect of dapagliflozin on other drugs: Dapagliflozin did not alter the pharmacokinetics of the coadministered drugs.

Pharmacodynamic interactions

Diuretics: BIOXIGA may add to the diuretic effect of loop diuretics and may increase the risk of dehydration and hypotension. Caution is recommended when BIOXIGA is co-administered with diuretics; particularly loop diuretics (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Drug-Food Interactions

Interactions with food have not been studied (see DOSAGE AND ADMINISTRATION, Dosing Considerations).

Drug-Herb Interactions

The effects of herbal products on the pharmacokinetics of dapagliflozin have not been studied.

Drug-Laboratory Interactions

Due to its mechanism of action, patients taking BIOXIGA will test positive for glucose in their urine. Monitoring glycemic control with 1, 5-AG assay is not recommended as measurements of 1,5AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

Drug-Lifestyle Interactions

The effects of smoking, diet, and alcohol use on the pharmacokinetics of dapagliflozin have not been specifically studied.

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be alerted to the elevated risk of adverse reactions related to reduced intravascular volume, such as postural dizziness, and to the risk of hypoglycemia when BIOXIGA is used as add-on therapy with insulin or an insulin secretagogue.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Concomitant use with insulin or an insulin secretagogue (e.g. sulfonylurea): When BIOXIGA is used as add-on therapy with insulin or an insulin secretagogue (e.g. sulfonylurea), a lower dose of insulin or the insulin secretagogue may be considered to reduce the risk of hypoglycemia (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

Diuretics: BIOXIGA should be used with caution in patients taking diuretics, particularly loop diuretics, due to the increased risk of adverse events due to volume depletion during coadministration.

Recommended Dose and Dosage Adjustment

The recommended starting dose of Dapagliflozin is 5 mg taken once daily at any time of the day with or without food. In patients tolerating Dapagliflozin 5 mg once daily and who require additional glycemic control, the dose can be increased to 10 mg daily.
In patients with evidence of volume depletion, this condition should be corrected prior to initiation of BIOXIGA (see WARNINGS AND PRECAUTIONS).

Renal impairment: The efficacy of BIOXIGA is dependent on renal function. Assessment of renal function is recommended prior to initiation of BIOXIGA therapy and periodically thereafter. No dosage adjustment for BIOXIGA is indicated in patients with mild renal impairment (eGFR ≥60 mL/min/1.73m^2).
BIOXIGA should be discontinued when eGFR is <60 mL/min/1.73m^2 (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).
BIOXIGA is contraindicated in patients with moderate to severe renal impairment (defined as eGFR <60 mL/min/1.73m^2) or ESRD (see CONTRAINDICATIONS).

Hepatic impairment: No dosage adjustment for BIOXIGA is necessary for patients with mild or moderate hepatic impairment. BIOXIGA exposure is increased in patients with severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics). Therefore, BIOXIGA is not recommended for use in this population.

Pediatrics (<18 years of age): Safety and effectiveness of BIOXIGA in pediatric and adolescent patients have not been established. Therefore, BIOXIGA should not be used in this population.

Geriatrics (≥65 years of age): No dosage adjustment for BIOXIGA is required based on age; however renal function and risk of volume depletion should be taken into account (see WARNINGS AND PRECAUTIONS).

Missed Dose

If a dose of BIOXIGA is missed, it should be taken as soon as the patient remembers. A double dose of BIOXIGA should not be taken on the same day.

OVERDOSAGE

It is reasonable to employ supportive measures, as dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not been studied.

STORAGE CONDITION

- Store in a cool, dark & dry place.
- Store below 30°C.
- Keep out of reach of children.

PRESENTATION- Dapagliflozin 10mg Tablets

PACKING- 1*10 TAB

For the use only of a Registered Medical Practitioner or Hospital or a Laboratory

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