ינואר 2023

רופא/ה נכבד/ה
רוקח/ת נכבד/ה שלום רב,

<u>פרסום עדכון בעלוני התכשירים</u>

Xigduo XR 5mg/500mg Extended release Tablets
Xigduo XR 5mg/1000mg Extended release Tablets
Xigduo XR 10mg/500mg Extended release Tablets
Xigduo XR 10mg/1000mg Extended release Tablets

הרכב:

XIGDUO XR is available for oral administration as tablets containing the equivalent of 5 mg dapagliflozin as dapagliflozin propanediol and 500 mg metformin hydrochloride (XIGDUO XR 5 mg/500 mg), the equivalent of 5 mg dapagliflozin as dapagliflozin propanediol and 1000 mg metformin hydrochloride (XIGDUO XR 5 mg/1000 mg), the equivalent of 10 mg dapagliflozin as dapagliflozin propanediol and 500 mg metformin hydrochloride (XIGDUO XR 10 mg/500 mg), or the equivalent of 10 mg dapagliflozin as dapagliflozin propanediol and 1000 mg metformin hydrochloride (XIGDUO XR 10 mg/1000 mg).

חברת אסטרהזניקה ישראל מבקשת להודיע על עדכון עלוני התכשיר בהתאם להוראות משרד הבריאות בתאריך **ינואר 2023.**

<u>התוויה:</u>

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

<u>העדכונים המהותיים בעלון לרופא הינם:</u>

Warnings and Precautions

Lactic acidosis

There have been post-marketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension, and resistant bradyarrhythmias have occurred with severe acidosis Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5mmol/L), anion gap acidosis (without evidence of (ketonuria or

ketonemia)), and an increased lactate: pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis especially in patients at risk.

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

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

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue XIGDUO XR and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment: The post-marketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include:

Before initiating XIGDUO XR, obtain an estimated glomerular filtration rate (eGFR).

- XIGDUO XR is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2.
- Obtain an eGFR at least annually in all patients taking XIGDUO XR. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Drug Interactions: The concomitant use of XIGDUO XR with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation (e.g., cationic drugs). Therefore, consider more frequent monitoring of patients.

Age 65 or Greater: The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.

Radiological Studies with Contrast: Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop XIGDUO XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart XIGDUO XR if renal function is stable.

Surgery and Other Procedures: Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. XIGDUO XR should be temporarily discontinued while patients have restricted food and fluid intake.

~~Hypotension~~

~~Dapagliflozin causes intravascular volume contraction. Symptomatic hypotension can occur after initiating dapagliflozin, particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics.~~

~~Before initiating XIGDUO XR in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms of hypotension after initiating therapy.~~

Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in post-marketing surveillance in patients with type 1 and type 2 diabetes mellitus taking sodium glucose co-transporter-2 (SGLT2) inhibitors, including dapagliflozin. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. Fatal cases of ketoacidosis have been reported in patients taking dapagliflozin. XIGDUO XR is not indicated for the treatment of patients with type 1 diabetes mellitus.

Volume Depletion

Dapagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including dapagliflozin. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating XIGDUO XR in patients with one or more of these characteristics, assess volume status and renal function. Monitor for signs and symptoms of hypotension and renal function after initiating therapy.

~~Acute Kidney Injury and Impairment in Renal Function~~

~~Dapagliflozin causes intravascular volume contraction, and can cause acute kidney injury. There have been postmarketing reports of acute kidney injury, some requiring hospitalization~~

and dialysis, in patients receiving dapagliflozin. some reports involved patients younger than 65 years of age.

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

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

Use of XIGDUO XR is not recommended when the eGFR is less than 45 mL/min/1.73 m^2.

XIGDUO XR is contraindicated in patients with an eGFR below 30 mL/min/1.73 m^2.

Adverse Reactions

Table 3: adverse Reactions Related to Volume Depletion[1] in Clinical Studies with Dapagliflozin

	Pool of 12 Placebo-Controlled Studies			Pool of 13 Placebo-Controlled Studies	
	Pool of 12 Placebo-Controlled Studies			Pool of 13 Placebo-Controlled Studies	
	Placebo	Dapagliflozin 5 mg	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg
Overall population N (%)	N=1393 5 (0.4%)	N=1145 7 (0.6%)	N=1193 9 (0.8%)	N=2295 17 (0.7%)	N=2360 27 (1.1%)
Patient Subgroup n (%)					
Patients on loop diuretics	n=55 1 (1.8%)	n=40 0	n=31 3 (9.7%)	n=267 4 (1.5%)	n=236 6 (2.5%)

~~Patients with moderate renal impairment with eGFR ≥30 and <60 mL/min/1.73 m²~~	~~n=107~~ ~~2 (1.9%)~~	~~n=107~~ ~~1 (0.9%)~~	~~n=89~~ ~~1 (1.1%)~~	~~n=268~~ ~~4 (1.5%)~~	~~n=265~~ ~~5 (1.9%)~~
~~Patients ≥65 years of age~~	~~n=276~~ ~~1 (0.4%)~~	~~n=216~~ ~~1 (0.5%)~~	~~n=204~~ ~~3 (1.5%)~~	~~n=711~~ ~~6 (0.8%)~~	~~n=665~~ ~~11 (1.7%)~~

~~1. Volume depletion includes reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension.~~

	Pool of 12 Placebo-Controlled Studies			**Pool of 13 Placebo-Controlled Studies**		**DECLARE Study**	
	Placebo	**Dapagliflozin 5 mg**	**Dapagliflozin 10 mg**	**Placebo**	**Dapagliflozin 10 mg**	**Placebo**	**Dapagliflozin 10 mg**
Overall population N (%)	N=1393 5 (0.4%)	N=1145 7 (0.6%)	N=1193 9 (0.8%)	N=2295 17 (0.7%)	N=2360 27 (1.1%)	N=8569 207 (2.4%)	N=8574 213 (2.5%)
Patient Subgroup n (%)							
Patients on loop diuretics	n=55 1 (1.8%)	n=40 0	n=31 3 (9.7%)	n=267 4 (1.5%)	n=236 6 (2.5%)	n=934 57 (6.1%)	n=866 57 (6.6%)
Patients with moderate renal impairment with eGFR ≥≥30 and <60 mL/min/1.73 m^2	n=107 2 (1.9%)	n=107 1 (0.9%)	n=89 1 (1.1%)	n=268 4 (1.5%)	n=265 5 (1.9%)	n=658 30 (4.6%)	n=604 35 (5.8%)
Patients ≥≥65 years of age	n=276 1 (0.4%)	n=216 1 (0.5%)	n=204 3 (1.5%)	n=711 6 (0.8%)	n=665 11 (1.7%)	n=3950 121 (3.1%)	n=3948 117 (3.0%)

* Volume depletion includes reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension.

Impairment of Renal Function

Use of dapagliflozin was associated with increases in serum creatinine and decreases in eGFR (see Table 4). In patients with normal or mildly impaired renal function at baseline, serum creatinine and eGFR returned to baseline values at Week 24. Renal-related adverse reactions, including renal failure and blood creatinine increase, were more frequent in patients treated with dapagliflozin (see Table 5). Elderly patients and patients with impaired renal function were more susceptible to these adverse reactions (see Table 5). Sustained decreases in eGFR were seen in patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2).

Table 4: Changes in Serum Creatinine and eGFR Associated with Dapagliflozin in the Pool of 12 Placebo-Controlled Studies and Moderate Renal Impairment Studies

		Pool of 12 Placebo-Controlled Studies		
		Placebo N=1393	Dapagliflozin 5 mg N=1145	Dapagliflozin 10 mg N=1193
Baseline Mean	Serum Creatinine (mg/dL)	0.853	0.860	0.847
	eGFR (mL/min/1.73 m^2)	86.0	85.3	86.7
Week 1 Change	Serum Creatinine (mg/dL)	−0.003	0.029	0.041
	eGFR (mL/min/1.73 m^2)	0.4	−2.9	−4.1
Week 24 Change	Serum Creatinine (mg/dL)	−0.005	−0.001	0.001
	eGFR (mL/min/1.73 m^2)	0.8	0.8	0.3
		Moderate Renal Impairment Study (eGFR 30 to less than 60 mL/min/1.73 m^2)		
		Placebo N=84	Dapagliflozin 5 mg N=83	Dapagliflozin 10 mg N=85
Baseline Mean	Serum Creatinine (mg/dL)	1.46	1.53	1.52
	eGFR (mL/min/1.73 m^2)	45.6	44.2	43.9
Week 1 Change	Serum Creatinine (mg/dL)	0.01	0.13	0.18
	eGFR (mL/min/1.73 m^2)	0.5	−3.8	−5.5
Week 24 Change	Serum Creatinine (mg/dL)	0.02	0.08	0.16

	eGFR (mL/min/1.73 m^2)	0.03	−4.0	−7.4
Week 52 Change	Serum Creatinine (mg/dL)	0.10	0.06	0.15
	eGFR (mL/min/1.73 m^2)	−2.6	−4.2	−7.3

		Moderate Renal Impairment Study (eGFR 45 to less than 60 mL/min/1.73 m^2)	
		Placebo N=161	Dapagliflozin 10 mg N=160
Baseline Mean	Serum Creatinine (mg/dL)	1.25	1.25
	eGFR (mL/min/1.73 m^2)	53.6	53.3
Week 4 Change	Serum Creatinine (mg/dL)	-0.02	0.09
	eGFR (mL/min/1.73 m^2)	1.3	-3.8
Week 12 Change	Serum Creatinine (mg/dL)	-0.02	0.08
	eGFR (mL/min/1.73 m^2)	1.5	-3.2
Week 24 Change	Serum Creatinine (mg/dL)	-0.003	0.06
	eGFR (mL/min/1.73 m^2)	0.8	-2.0

Table 5: Proportion of Patients with at Least One Renal Impairment-Related Adverse Reaction

	Pool of 6 Placebo-Controlled Studies (up to 104 weeks)[1]			Pool of 9 Placebo-Controlled Studies (up to 104 weeks)[2]	
Baseline Characteristic	**Placebo**	**Dapagliflozin 5 mg**	**Dapagliflozin 10 mg**	**Placebo**	**Dapagliflozin 10 mg**
Overall population Patients (%) with at least one event	n=785 13 (1.7%)	n=767 14 (1.8%)	n=859 16 (1.9%)	n=1956 82 (4.2%)	n=2026 136 (6.7%)
65 years of age and older Patients (%) with at least one event	n=190 4 (2.1%)	n=162 5 (3.1%)	n=159 6 (3.8%)	n=655 52 (7.9%)	n=620 87 (14.0%)
eGFR ≥30 and <60 mL/min/1.73 m^2 Patients (%) with at least one event	n=77 5 (6.5%)	n=88 7 (8.0%)	n=75 9 (12.0%)	n=249 40 (16.1%)	n=251 71 (28.3%)

65 years of age and older and eGFR ≥30 and <60 mL/min/1.73 m² Patients (%) with at least one event	n=41 2 (4.9%)	n=43 3 (7.0%)	n=35 4 (11.4%)	n=141 27 (19.1%)	n=134 47 (35.1%)

1. Subset of patients from the pool of 12 placebo-controlled studies with long-term extensions.
2. Subset of patients from the pool of 13 placebo-controlled studies with long-term extensions.

In the pool of 12 clinical studies, a subgroup analysis assessed thesafety of patients with (eGFR between 30 to less than 60 mL/min/1.73 m^2). At Week 24, the safety was similar to that seen in the overall program, although a higher proportion of patients had at least one event related to renal impairment or failure.

Fractures

In a study of patients with eGFR 30 to less than 60 mL/min/1.73 m^2

13 patients experienced bone fractures for treatment durations up to 104 weeks. No fractures occurred in the placebo group, 5 occurred in the dapagliflozin 5 mg group, and 8 occurred in the dapagliflozin 10 mg group. Eight of these 13 fractures were in patients who had a baseline eGFR of 30 to 45 mL/min/1.73 m^2. Ten of the 13 fractures were reported within the first 52 weeks. There was no apparent pattern with respect to the anatomic site of fracture.

In the DECLARE study, severe events of hypoglycemia were reported in 58 (0.7%) out of 8574 patients treated with dapagliflozin 10 mg and 83 (1.0%) out of 8569 patients treated with placebo.

Genital Mycotic Infections

In the glycemic control studies, genital mycotic infections were more frequent with dapagliflozin treatment. Genital mycotic infections were reported in 0.9% of patients on placebo, 5.7% on dapagliflozin 5 mg, and 4.8% on dapagliflozin 10 mg, in the 12-study placebo-controlled pool. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with dapagliflozin 10 mg. Infections were more frequently reported in females than in males (see Table 2). The most frequently reported genital mycotic infections were vulvovaginal mycotic infections in females and balanitis in males. Patients with a history of genital mycotic infections were more likely to have a genital mycotic infection during the study than those with no prior history (10.0%, 23.1%, and 25.0% versus 0.8%, 5.9%, and 5.0% on placebo, dapagliflozin 5 mg, and dapagliflozin 10 mg, respectively). In the DECLARE study, serious genital mycotic infections were reported in <0.1% of patients treated with dapagliflozin 10 mg and <0.1% of patients treated with placebo. Genital mycotic infections that caused study drug discontinuation were reported in 0.9% of patients treated with dapagliflozin 10 mg and <0.1% of patients treated with placebo.

Ketoacidosis
In the DECLARE study, events of diabetic ketoacidosis (DKA) were reported in 27 out of 8574 patients in the dapagliflozin-treated group and in 12 out of 8569 patients in the placebo group. The events were evenly distributed over the study period.

Laboratory Tests

Increases in Serum Creatinine and Decreases in eGFR

Dapagliflozin

Initiation of SGLT2 inhibitors, including dapagliflozin, causes a small increase in serum creatinine and decrease in eGFR. These changes in serum creatinine and eGFR generally occur within two weeks of starting therapy and then stabilize regardless of baseline kidney function. Changes that do not fit this pattern should prompt further evaluation to exclude the possibility of acute kidney injury. In two studies that included patients with type 2 diabetes mellitus with moderate renal impairment, the acute effect on eGFR reversed after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with dapagliflozin.

~~***Increase in Serum Inorganic Phosphorus***~~

~~**Dapagliflozin**~~

~~In the pool of 13 placebo-controlled studies, increases from baseline in mean serum phosphorus levels were reported at Week 24 in dapagliflozin 10 mg treated patients compared with placebo-treated patients (mean increases of 0.13 mg/dL versus −0.04 mg/dL, respectively). Higher proportions of patients with marked laboratory abnormalities of hyperphosphatemia (≥5.6 mg/dL if age 17-65 or ≥5.1 mg/dL if age ≥66) were reported in the dapagliflozin 10 mg group versus the placebo group at Week 24 (1.7% versus 0.9%, respectively).~~

Drug interactions

Table 5: Clinically Relevant Interactions with XIGDUO XR

Carbonic Anhydrase Inhibitors	
Clinical Impact	Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with XIGDUO XR may increase the risk for lactic acidosis.
Intervention	Consider more frequent monitoring of these patients.
Drugs that Reduce Metformin Clearance	
Clinical	Concomitant use of drugs that interfere with common renal tubular transport

Table 5: Clinically Relevant Interactions with XIGDUO XR

Impact	systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2]/multidrug and toxin extrusion [MATE] inhibitors, such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis.
Intervention	Consider the benefits and risks of concomitant use.
Alcohol	
Clinical Impact	Alcohol is known to potentiate the effect of metformin on lactate metabolism.
Intervention	Warn patients against excessive alcohol intake while receiving XIGDUO XR.
Insulin or Insulin Secretagogues	
Clinical Impact	The risk of hypoglycemia may be increased when XIGDUO XR is used concomitantly with insulin or insulin secretagogues (e.g., sulfonylurea) *[see Warnings and Precautions (5.5)]*.
Intervention	Concomitant use may require lower doses of insulin or the insulin secretagogue to reduce the risk of hypoglycemia.
Drugs Affecting Glycemic Control	
Clinical Impact	Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These medications include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid.
Intervention	When such drugs are administered to a patient receiving XIGDUO XR, observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving XIGDUO XR, observe the patient closely for hypoglycemia.
Lithium	
Clinical Impact	Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations
Intervention	Monitor serum lithium concentration more frequently during XIGDUO XR initiation and dosage changes.

Table 5: Clinically Relevant Interactions with XIGDUO XR

Positive Urine Glucose Test	
Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
Intervention	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
Clinical Impact	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
Intervention	Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control.

Use in specific populations

Pregnancy

Risk Summary

Based on animal data showing adverse renal effects, XIGDUO XR is not recommended during the second and third trimesters of pregnancy.

~~Limited data with XIGDUO XR or dapagliflozin in pregnant women are not sufficient to determine drug-associated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy.~~

~~In animal studies, adverse renal pelvic and tubule dilatations, that were not fully reversible, were observed in rats when dapagliflozin was administered during a period of renal development corresponding to Based on animal data showing adverse renal effects, XIGDUO XR is not recommended during the second and third trimesters of pregnancy.~~

Geriatric use

No XIGDUO XR dosage change is recommended based on age. More frequent assessment of renal function is recommended in elderly patients.

Renal impairment

Initiation of XIGDUO XR is not recommended in patients with an eGFR below 45 mL/min/1.73 m^2 and is contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end stage renal disease or patients on dialysis.

~~In clinical studies (dapagliflozin was associated with increases in serum creatinine and decreases in eGFR. Use of dapagliflozin is not recommended when eGFR is less than 45 mL/min/1.73 m^2 and is contraindicated in patients with renal impairment. (eGFR less than 30 mL/min/1.73 m^2) or ESRD.~~

~~patients with moderate renal impairment (an eGFR of 45 to less than 60 mL/min/1.73 m^2, and an eGFR of 30 to less than 60 mL/min/1.73 m^2) *[see Clinical Studies (14.4)]*. The safety profile of dapagliflozin in the study of patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 was similar to the general population. of patients with type 2 diabetes. Although patients in the dapagliflozin arm had reduction in eGFR compared to the placebo arm, eGFR generally returned towards baseline after treatment discontinuation.~~

Dapagliflozin 10 mg was evaluated in two glycemic control studies that included patients with moderate renal impairment (an eGFR of 45 to less than 60 mL/min/1.73 m^2, and an eGFR of 30 to less than 60 mL/min/1.73 m^2). Patients with diabetes and renal impairment using dapagliflozin 10 mg are more likely to experience hypotension and may be at higher risk for acute kidney injury secondary to volume depletion. In the study of patients with an eGFR 30 to less than 60 mL/min/1.73 m^2, 13 patients receiving dapagliflozin experienced bone fractures compared to none receiving placebo. Use of dapagliflozin 10 mg for glycemic control in patients without established CV disease or CV risk factors is not recommended when eGFR is less than 45 mL/min/1.73 m^2.

Overdosage

Dapagliflozin

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

Metformin hydrochloride

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

Clinical Pharmacology

Mechanism of Action

~~*XIGDUO XR*~~

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

Dapagliflozin

Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose ~~and lowers the renal threshold for glucose~~, and thereby ~~increases~~ promotes urinary glucose excretion. Dapagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to, lowering both pre- and afterload of the heart and downregulation of sympathetic activity, and decreased intraglomerular pressure which is believed to be mediated by increased tubuloglomerular feedback.

Metformin hydrochloride

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. ~~Metformin does not produce hypoglycemia in either patients with type 2 diabetes or in healthy subjects, except in unusual circumstances, and does not cause hyperinsulinemia.~~ With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.

Pharmacodynamics

General

Dapagliflozin

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following the administration of dapagliflozin (see Figure 1). Dapagliflozin doses of 5 or 10 mg per day in patients with type 2 diabetes mellitus for 12 weeks resulted in excretion of approximately 70 grams of glucose in the urine per day. A near maximum glucose excretion was observed at the dapagliflozin daily dose of 20 mg. This urinary glucose excretion with dapagliflozin also results in increases in urinary volume. After discontinuation of dapagliflozin, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg dose.

Pharmacokinetics

XIGDUO XR

~~XIGDUO XR combination tablets are considered to be bioequivalent to coadministration of corresponding doses of dapagliflozin (FARXIGA™) and metformin hydrochloride extended-release (GLUCOPHAGE® XR) administered together as individual tablets.~~

The administration of XIGDUO XR in healthy subjects after a standard meal compared to the fasted state resulted in the same extent of exposure for both dapagliflozin and metformin extended-release. Compared to the fasted state, the standard meal resulted in 35% reduction and a delay of 1 to 2 hours in the peak plasma concentrations of dapagliflozin. This effect of food is not considered to be clinically meaningful. Food has no relevant effect on the pharmacokinetics of metformin when administered as XIGDUO XR combination tablets.

Specific Populations

Renal Impairment

Metformin hydrochloride

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

Hepatic Impairment

~~*XIGDUO XR*~~

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

Geriatric

Metformin hydrochloride

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

~~XIGDUO XR should not be initiated in patients of any age unless measurement of creatinine clearance demonstrates that renal function is only normal or mildly impaired.~~

Nonclinical Toxicology

Dapagliflozin

Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in 2-year carcinogenicity studies. Oral doses in mice consisted of 5, 15, and 40 mg/kg/day in males and 2, 10, and 20 mg/kg/day in females, and oral doses in rats were 0.5, 2, and 10 mg/kg/day

for both males and females. The highest doses evaluated in mice were approximately 72 times (males) and 105 times (females) the clinical dose of 10 mg/day based on AUC exposure. In rats, the highest dose was approximately 131 times (males) and 186 times (females) the clinical dose of 10 mg perday based on AUC exposure.
Dapagliflozin was negative in the Ames mutagenicity assay and was positive in a series of *in vitro* clastogenicity assays in the presence of S9 activation and at concentrationsgreater than or equal to 100 µg/mL. Dapagliflozin was negative for clastogenicity in a series of *in vivo* studies evaluating micronuclei or DNA repair in rats at exposure multiplesgreater than2100 times the clinical dose.

~~There was no carcinogenicity or mutagenicity signal in animal studies, suggesting that dapagliflozin does not represent a genotoxic risk to humans.~~

Clinical Studies

Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

Dapagliflozin Effect on Cardiovascular Events (DECLARE, NCT01730534) was an international, multicenter, randomized, double-blind, placebo-controlled, clinical study conducted to determine the effect of dapagliflozin 10 mg relative to placebo on cardiovascular (CV) outcomes when added to current background therapy. All patients had type 2 diabetes mellitus and either established CV disease or two or more additional CV risk factors (age ≥55 years in men or ≥60 years in women and one or more of dyslipidemia, hypertension, or current tobacco use). Concomitant antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators, to ensure participants were treated according to the standard care for these diseases.
Of 17160 randomized patients, 6974 (40.6%) had established CV disease and 10186 (59.4%) did not have established CV disease. A total of 8582 patients were randomized to dapagliflozin 10 mg, 8578 to placebo, and patients were followed for a median of 4.2 years.
Approximately 80% of the trial population was White, 4% Black or African American, and 13% Asian. The mean age was 64 years, and approximately 63% were male.
Mean duration of diabetes was 11.9 years and 22.4% of patients had diabetes for less than 5 years. Mean eGFR was 85.2 mL/min/1.73 m^2. At baseline, 23.5% of patients had microalbuminuria (UACR ≥30 to ≤300 mg/g) and 6.8% had macroalbuminuria (UACR >300 mg/g). Mean HbA1c was 8.3% and mean BMI was 32.1 kg/m^2. At baseline, 10% of patients had a history of heart failure. Most patients (98.1%) used one or more antihyperglycemic medications at baseline. 82.0% of the patients were being treated with metformin, 40.9% with insulin, 42.7% with a sulfonylurea, 16.8% with a DPP4 inhibitor, and 4.4% with a GLP-1 receptor agonist.

Approximately 81.3% of patients were treated with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, 75.0% with statins, 61.1% with antiplatelet therapy, 55.5% with acetylsalicylic acid, 52.6% with beta-blockers, 34.9% with calcium channel blockers, 22.0% with thiazide diuretics, and 10.5% with loop diuretics.

A Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio (HR) of the composite of CV death, myocardial infarction (MI), or ischemic stroke (MACE) and if non-inferiority was

demonstrated, to test for superiority on the two primary endpoints: 1) the composite of hospitalization for heart failure or CV death, and 2) MACE.
The incidence rate of MACE was similar in both treatment arms: 2.30 MACE events per 100 patient-years on dapagliflozin vs 2.46 MACE events per 100 patient-years on placebo. The estimated hazard ratio of MACE associated with dapagliflozin relative to placebo was 0.93 with a 95% CI of (0.84, 1.03). The upper bound of this confidence interval, 1.03, excluded the prespecified non-inferiority margin of 1.3.
Dapagliflozin 10 mg was superior to placebo in reducing the incidence of the primary composite endpoint of hospitalization for heart failure or CV death (HR 0.83 [95% CI 0.73, 0.95]).
The treatment effect was due to a significant reduction in the risk of hospitalization for heart failure in subjects randomized to dapagliflozin 10 mg (HR 0.73 [95% CI 0.61, 0.88]), with no change in the risk of CV death (Table 15 and Figures 4 and 5).

Table 15: Treatment Effects for the Primary Endpoints* and their Components* in the DECLARE Study

	Patients with events n(%)		
Efficacy Variable (time to first occurrence)	**Dapagliflozin 10 mg N=8582**	**Placebo N=8578**	**Hazard Ratio (95% CI)**
Primary Endpoints			
Composite of Hospitalization for Heart Failure, CV Death†	417 (4.9)	496 (5.8)	0.83 (0.73, 0.95)
Composite Endpoint of CV Death, MI, Ischemic Stroke	756 (8.8)	803 (9.4)	0.93 (0.84, 1.03)
Components of the composite endpoints‡			
Hospitalization for Heart Failure	212 (2.5)	286 (3.3)	0.73 (0.61, 0.88)
CV Death	245 (2.9)	249 (2.9)	0.98 (0.82, 1.17)
Myocardial Infarction	393 (4.6)	441 (5.1)	0.89 (0.77, 1.01)
Ischemic Stroke	235 (2.7)	231 (2.7)	1.01 (0.84, 1.21)

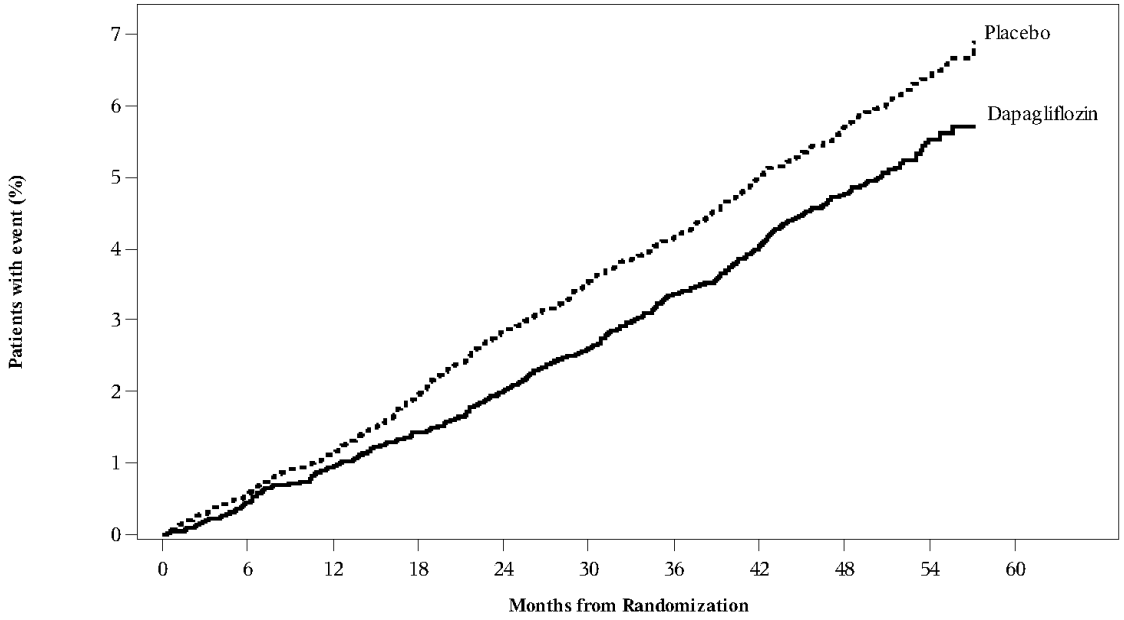
N=Number of patients, CI=Confidence interval, CV=Cardiovascular, MI=Myocardial infarction, eGFR=estimated glomerular filtration rate, ESRD=End-stage renal disease

* Full analysis set.

† p-value =0.005 versus placebo.

‡ total number of events presented for each component of the composite endpoints.

Figure 4: Time to First Occurrence of Hospitalization for Heart Failure or CV Death in the DECLARE Study

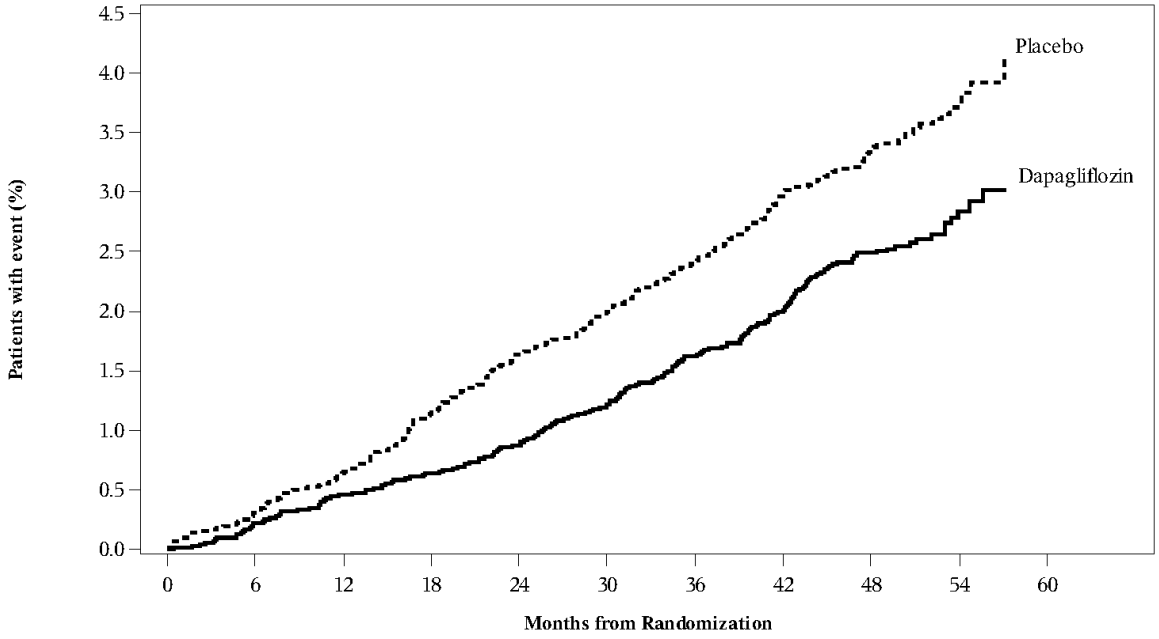


Patients at risk

Dapagliflozin:	8582	8517	8415	8322	8224	8110	7970	7497	5445	1626
Placebo:	8578	8485	8387	8259	8127	8003	7880	7367	5362	1573

אסטרהזניקה (ישראל) בע"מ, רח' עתירי ידע 1 כפר סבא 4464301
טלפון 073-2226099 פקס 09-7406527

Figure 5: Time to First Occurrence of Hospitalization for Heart Failure in the DECLARE Study



Patients at risk

Dapagliflozin:	8582	8509	8403	8315	8218	8101	7965	7489	5439	1626
Placebo:	8578	8482	8380	8256	8121	7998	7874	7360	5358	1572

אסטרהזניקה (ישראל) בע"מ, רח' עתירי ידע 1 כפר סבא 4464301
טלפון 073-2226099 פקס 09-7406527

עדכונים מהותיים בעלון לצרכן:

למה מיועדת התרופה?

קסיגדו XR ניתנת לטיפול בסוכרת מסוג 2 במבוגרים (גיל 18 ומעלה), בשילוב עם דיאטה ופעילות גופנית.
קסיגדו XR מיועדת לשיפור איזון רמות הסוכר בדם, כאשר טיפול בדפהגליפלוזין או וגם במטפורמין ~~בנפרד לא הביאו לאיזון רמות הסוכר בדם~~ מתאים

אזהרות מיוחדות הנוגעות לשימוש בקסיגדו XR

חמצת לקטית (lactic acidosis): המרכיב הפעיל מטפורמין בקסיגדו XR עלול לגרום לתופעת לוואי נדירה אך חמורה הנקראת חמצת לקטית. חמצת לקטית מאופיינת ברמות גבוהות של חומצה לקטית בדם, העלולה לגרום למוות. חמצת לקטית דורשת טיפול רפואי דחוף בבית חולים.

הפסק נטילת קסיגדו XR ופנה לרופא באופן מיידי אם יש לך אחד מהתסמינים הבאים, שיכול להיות סימן לחמצת לקטית:

- תחושת קור בכפות הרגליים והידיים
- סחרחורת או תחושה שהנך עומד להתעלף
- דופק איטי או לא רגיל
- תחושת חולשה ועייפות רבה
- כאבי שרירים לא רגילים
- קשיי נשימה
- ישנוניות לא רגילה או שינה ארוכה מהרגיל
- כאב בטן, בחילה או הקאה

מרבית האנשים שסבלו מחמצת לקטית כתוצאה מנטילת מטפורמין (מרכיב פעיל בקסיגדו XR), סבלו מבעיות נוספות, שבשילוב עם נטילת המטפורמין, גרמו לחמצת הלקטית.

פנה לרופא במידה ואתה סובל מאחד מהמצבים הבאים מאחר ויש לך סיכוי גבוה יותר לפתח חמצת לקטית עם קסיגדו XR:

- סובל מבעיות כליה חמורות, או הכליות מושפעות מחומר ניגוד שהוזרק לך לצורך בדיקת רנטגן.
- סובל מבעיות בכבד.
- הנך שותה אלכוהול לעיתים קרובות מאוד או שותה אלכוהול בכמות גדולה בזמן קצר.
- במצב של התייבשות (מאבד כמות גדולה של נוזלים). מצב זה יכול לקרות אם הנך חולה עם חום, עם הקאות או עם שלשול. התייבשות יכולה להגרם גם אם אתה מרבה להזיע בעת פעילות גופנית ואינך שותה מספיק נוזלים.
- עובר ניתוח.
- סובל מתסמינים חדשים או החמרה בתסמינים של תסמיני אי ספיקת לב כגון קוצר נשימה, הצטברות נוזלים או נפיחות ברגליים
- עובר התקף לב, זיהום חמור או שבץ.
- הנך בן 65 ומעלה
- **לפני או במהלך הטיפול בקסיגדו XR ספר לרופא, לרוקח או לאחות אם:**
  - הינך סובל מסוכרת מסוג 1 או שיש או היה לך קטואצידוזיס סוכרתי.
  - הנך מטופל במקביל באינסולין וחלה הפחתה חדה במינון האינסולין אותו הנך נוטל.
  - יש לך בעיות בכליות,
  - יש לך בעיות בכבד.
  - יש לך היסטוריה של ~~דלקת~~ זיהום בנרתיק או ~~וגינלית או דלקת~~ בפין.
  - יש לך היסטוריה של דלקות בדרכי השתן או בעיות במתן שתן.

אסטרהזניקה (ישראל) בע"מ, רח' עתירי ידע 1 כפר סבא 4464301
טלפון 073-2226099 פקס 09-7406527

- הנך סובל מבעיות בלב, כולל אי ספיקת לב.
- הינך בן 65 ומעלה
- הנך אוכל פחות או שיש שינוי בתזונה שלך.
- יש לך או היו לך בעיות בלבלב, כולל דלקת בלבלב או ניתוח בלבלב.
- שותה אלכוהול לעיתים קרובות מאוד, או שותה אלכוהול בכמות רבה בפרק זמן קצר.
- הנך עומד לקבל זריקת צבע או חומר ניגודי לבדיקת רנטגן. במקרה זה יתכן ויהיה עליך להפסיק את השימוש בקסיגדו XR לזמן קצר. פנה אל הרופא לקבלת הנחיותיו מתי להפסיק נטילת קסיגדו XR ומתי עליך לחזור לקבלת הטיפול ולהמשיך הטיפול בקסיגדו XR.
- אתה עומד לעבור ניתוח ולא תוכל לאכול או לשתות הרבה. ייתכן והרופא יורה להפסיק את הטיפול בקסיגדו XR לפני הניתוח. פנה אל הרופא לקבלת הנחיותיו מתי להפסיק נטילת קסיגדו XR ומתי עליך לחזור לקבלת הטיפול ולהמשיך הטיפול בקסיגדו XR.
- יש לך רמות נמוכות של ויטמין B12 בדם.
- הנך טרום תקופת הפסקת הווסת ואינך מקבלת ווסת על בסיס קבוע או כלל לא. קסיגדו XR עלול לגרום לשחרור של ביצית מהשחלה (ביוץ) וזה עלול להגביר את הסיכוי להכנס להריון. פני אל הרופא מיד עם הכניסה להריון במהלך הטיפול בקסיגדו XR.
- הינך סובל מזיהומים בדרכי השתן לעיתים קרובות. בעת השימוש בתרופה קיים סיכון מוגבר לזיהום בדרכי השתן (יתכן והרופא יפסיק זמנית את הטיפול בתרופה עם הופעת זיהום חריף בדרכי השתן).

אינטראקציות/תגובות בין תרופתיות

אם אתה לוקח, או אם לקחת לאחרונה, תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח. ~~במיוחד יש ליידע אם אתה לוקח תרופות:~~

~~משתנות (דיורטיות),~~

~~לטיפול בשחפת או במניעתה (כגון ריפמפין)~~

~~לטיפול בפירכוסים (כגון פניטואין)~~

~~לטיפול בבעיות לב (כגון דיגוקסין)~~

~~לטיפול באסטמה (מרחיבי סימפונות מקבוצת בטא-2 אגוניסטים)~~

~~לטיפול בבעיות עיכול (כגון סימטידין)~~

~~קורטיקוסטרואידים לטיפול בדלקות, במחלות כמו אסטמה ודלקת פרקים~~

~~להורדת רמת הסוכר בדם כמו אינסולין או תרופת "סולפונילאוריאה". הרופא יכול להנחות אותך להפחתת מינון של תרופות אלו למניעת ירידת יתר של הסוכר בדם (היפוגליקמיה).~~

קסיגדו XR עלול להשפיע על הפעילות של תרופות אחרות ותרופות אחרות יכולות להשפיע על הפעילות של קסיגדו XR

הריון והנקה:

אם את בהריון, מתכננת הריון, חושבת שאת בהריון, יש להיוועץ ברופא לפני השימוש בתרופה.

קסיגדו XR יכול לגרום נזק לעובר. דברי עם הרופא לגבי הדרך הטובה ביותר לטיפול באיזון רמת הסוכר בדם.

אם הנך מיניקה או מתכננת להניק יש להיוועץ ברופא לפני השימוש בתרופה. לא ידוע אם קסיגדו XR עובר לחלב. דברי עם הרופא לגבי הדרך הטובה ביותר להזין את תינוקך כשאת לוקחת קסיגדו XR. אין להניק אם הנך נוטלת קסיגדו XR

תופעות לוואי נוספות:

- התייבשות - איבוד גדול של נוזלים ומלחים מהגוף. התייבשות עלולה לגרום להרגשת סחרחורת, לעילפון, תחושה שהנך עומד להתעלפאו חולשה במיוחד בעת קימה (תת לחץ דם בעמידה). ישנם דווחים על פגיעה כלייתית פתאומית במטופלים עם סוכרת סוג 2 אשר לוקחים דאפהגליפלוזין, מרכיב פעיל בתוך קסיגדו XR.
- אתה עלול להיות בסיכון גבוה יותר להתייבשות אם:
  - ~~יש לך לחץ דם נמוך~~
  - אתה לוקח תרופות להורדת לחץ דם, כולל תרופות משתנות (דיורטיות)
  - הנך בגיל 65 או מבוגר יותר
  - אתה בדיאטת דלת מלח
  - יש לך בעיות בכליה

שוחח עם הרופא שלך מה ניתן לעשות על מנת למנוע התייבשות, כולל כמה נוזלים לשתות מידי יום. פנה לרופא מיידית במידה והנך מפחית את כמות האוכל או הנוזלים שאתה שותה, לדוגמא, אם אינך יכול לאכול או מתחיל לאבד נוזלי גוף, למשל, כתוצאה מהקאה, שלשול או משהות ממושכת מדי בשמש.

- זיהומים באזור הגניטלי (Fournier's gangrene/necrotising fasciitis of the perineum),

זיהום נדיר אך חמור ברקמות הרכות באברי המין או באזור בין איבר המין ופי הטבעת, תופעה נדירה מאד שעלולה להתרחש בנשים וגברים שנוטלים דאפהגליפלוזין, שהוא מרכיב פעיל בקסיגדו XR.

זיהום מסוג זה עלול להוביל לאשפוז, יתכן וידרוש מספר ניתוחים ועלול לגרום למוות.

יש לפנות לעזרה רפואית מידית במקרה של חום, תחושת חולשה מוגברת, עייפות או תחושה כללית רעה והנך מפתח אחד מהתסמינים הבאים: אודם, כאב, רגישות או נפיחות באיזור הגניטלי עד פי הטבעת.

תסמינים אלו עלולים להידרדר במהירות ולכן חשוב לפנות לעזרה רפואית במהירות.

מקרא לעדכונים המסומנים:
תוספת טקסט מהותי מסומנת בצבע כחול.
מחיקת טקסט מסומנת בקו חוצה בצבע אדום.

העלונים מפורסמים במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום.

אסטרהזניקה (ישראל) בע"מ, רח' עתירי ידע 1 כפר סבא 4464301
טלפון 073-2226099 פקס 09-7406527

בכבוד רב,
קארין קנבל דובסון
רוקחת ממונה
אסטרהזניקה (ישראל) בע״מ

אסטרהזניקה (ישראל) בע"מ, רח' עתירי ידע 1 כפר סבא 4464301
טלפון 073-2226099 פקס 09-7406527