אפריל 2020

רופא/ה נכבד/ה

רוקח/ת נכבד/ה שלום רב,

<u>פרסום עדכון בעלון לרופא של 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).

התוויה:

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.

חברת אסטרהזניקה ישראל מבקשת להודיע על עדכון עלון בהתאם להוראות משרד הבריאות בתאריך **אפריל 2020**

העדכונים המהותיים בעלון לרופא הם:

2.1 Prior to Initiation of XIGDUO XR

- Assess renal function before initiating XIGDUO XR ~~should be taken~~ therapy and periodically thereafter *[see Warnings and Precautions (5.1, 5.4)]*.
- In patients with volume depletion, correct this condition prior to initiation of XIGDUO XR *[see Warnings and Precautions (5.2), Use in Specific Populations (8.5)]*.

2.~~2~~ 3 Patients with Renal Impairment

No dosage adjustment for XIGDUO XR is ~~indicated~~ needed in patients with ~~mild renal impairment~~ an ~~(~~eGFR ~~of 60~~ greater than or equal to 45 mL/min/1.73 m^2 ~~or greater)~~.

~~Assessment of renal function is recommended prior to initiation of XIGDUO XR therapy and periodically thereafter.~~

~~XIGDUO XR should not be used in patients with moderate to severe renal impairment (defined as eGFR <60 mL/min/1.73 m^2 or CrCl <60 mL/min, or end-stage renal disease [ESRD]) [see *Contraindications (4)*, *Warnings and Precautions (5.3)*, *Adverse Reactions (6.1)*, and *Use in Specific Populations (8.6)*].~~
XIGDUO XR is not recommended in patients with an eGFR below 45 mL/min/1.73 m^2.

4 CONTRAINDICATIONS

XIGDUO XR is contraindicated in patients with:

- ~~Moderate to~~ severe renal impairment ~~(e.g., serum creatinine levels ≥1.5 mg/dL for men, ≥1.4 mg/dL for women, or (~~eGFR below 30 ~~<60~~ mL/min/1.73 m^2 ~~or CrCl <60 mL/min), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia~~ end stage renal disease or patients on dialysis [see *Warnings and Precautions (5.1~~3~~)*].
- History of a serious hypersensitivity reaction to dapagliflozin or hypersensitivity to metformin hydrochloride [see *Adverse Reactions (6.1)*].
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

~~Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with XIGDUO XR; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of~~ There have been post-marketing cases of metformin-associated lactic acidosis, ~~metformin plasma levels >5 µg/mL are generally found.~~

~~The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03~~ including fatal cases~~/1000 patient-years, with approximately 0.015 fatal~~. These cases~~/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake when taking metformin since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure [see *Warnings and Precautions (5.2, 5.3, 5.7, 5.8, 5.9, 5.13)*]~~.~~

~~The onset of lactic acidosis often is~~ had a subtle onset and were accompanied ~~only~~ by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, ~~increasing~~ or increased somnolence, ~~and nonspecific abdominal distress. There may be associated~~ ; however, hypothermia, hypotension, and resistant bradyarrhythmias ~~with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur [see *Warnings and Precautions (5.2)*]. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.~~ have accorred with severe acidosis

~~Levels of fasting venous plasma lactate above the upper limit of normal (ULN), but <5 mmol/L, in patients taking metformin do not necessarily indicate impending~~ Metformin-associated lactic acidosis ~~and may be explainable~~ was characterized by ~~other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling [see *Warnings and Precautions (5.10)*]~~.

elevated blood lactate concentrations (>5mmol/L), anion gap ~~Lactic~~ acidosis ~~should be suspected in any diabetic patient with metabolic acidosis lacking~~ (without evidence of ~~ketoacidosis~~ (ketonuria or ~~and~~ ketonemia).

~~Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with~~), 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 ~~who is taking~~ especially in patients at risk.

If metformin, ~~the drug should be discontinued immediately and~~ -associated lactic acidosis is suspected, general supportive measures ~~promptly~~ should be instituted. ~~Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions),~~ 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 ~~the~~ accumulated metformin. ~~Such management often results in prompt~~ - (metformin HCl 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 ~~[see *Contraindications (4)* and *Warnings and Precautions (5.2, 5.8, 5.9, 5.12, 5.13)*].~~

~~5.2~~ Hypoxic States

: Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute ~~congestive heart failure, acute~~ myocardial infarction, sepsis, and other conditions ~~characterized by~~ associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur ~~in patients on XIGDUO XR therapy, the drug should be promptly discontinued. .~~, discontinue XIGDUO XR.

~~5.3 Use in Patients with Renal Impairment~~

~~Metformin is known to be substantially excreted by~~ by

Excessive Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism~~kidney~~ and this may increase the risk of metformin ~~accumulation and~~ associated lactic acidosis ~~increases~~ Warn patients against excessive alcohol intake while receiving XIGDUO XR.

Hepatic Impairment : Patients with ~~the degree of~~ hepatic impairment have developed with cases of ~~renal function~~ metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. . Therefore, avoid use of XIGDUO XR ~~is contraindicated~~ in patients with ~~moderate to severe renal impairment [see *Contraindications (4)*]. Also, 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 [see *Adverse Reactions (6.1)*]~~ clinical or laboratory evidence of hepatic disease.

~~Before initiation of XIGDUO XR therapy, and at least annually thereafter, renal function should be assessed and verified as normal or mildly impaired. In patients in whom development of renal~~

~~impairment is anticipated (e.g., elderly), renal function should be assessed more frequently and XIGDUO XR discontinued if evidence of moderate to severe renal impairment is present.~~

5.3~~5~~ Ketoacidosis

Before initiating XIGDUO XR, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction and alcohol abuse. For patients who undergo scheduled surgery, consider temporarily discontinuing XIGDUO XR for at least 3 days prior to surgery *[see Clinical Pharmacology (12.2, 12.3)].*

~~In patients treated with XIGDUO XR~~ consider monitoring for ketoacidosis and temporarily discontinuing XIGDUO XR in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting XIGDUO XR.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue XIGDUO XR and seek medical attention immediately if signs and symptoms occur.

5.4 Acute Kidney Injury and Impairment in Renal Function

Dapagliflozin causes intravascular volume contraction *[see Warning and Precautions (5.1)]*, 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.

~~Elderly patients and patients with impaired renal function may be more susceptible to these changes. 6~~

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 *[see Adverse Reactions (6.1)]*. 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 *[see Dosage and Administration (2.3), Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.6)].*

~~5.6~~5.5 Urosepsis and Pyelonephritis

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including dapagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections; ~~therefore, temporary interruption of XIGDUO XR should be considered when treating pyelonephritis, urosepsis or severe urinary tract infections~~ . Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. ~~Consider risk to benefit in patient with history of recurrent urinary tract infections. Patients should be advised of an increased risk of urinary tract infections~~ [see *Adverse Reactions (6.2)*].

~~5.7 Impaired Hepatic Function~~

~~Metformin use in patients with impaired hepatic function has been associated with some cases of lactic acidosis. Therefore, XIGDUO XR should generally be avoided in patients with hepatic impairment.~~

~~5.8 Alcohol Intake~~

~~Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving XIGDUO XR.~~

~~5.9 Surgical Procedures~~

~~Use of XIGDUO XR should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal or mildly impaired.~~

~~5.10 Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes~~

~~A patient with type 2 diabetes, previously well controlled on XIGDUO XR, who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of lactic acidosis. Evaluation should include serum electrolytes, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If lactic acidosis occurs, XIGDUO XR must be stopped immediately and other appropriate corrective measures initiated.~~

~~5.12 Concomitant Medications Affecting Renal Function or Metformin Disposition~~

~~Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion [see *Drug Interactions (7.3)*], should be used with caution.~~

~~5.13 Radiologic Studies with Intravascular Iodinated Contrast Materials~~

~~Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, XIGDUO XR should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal or mildly impaired.~~

~~5.14~~5.7 Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier's Gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including dapagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with XIGDUO XR presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue XIGDUO XR, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

~~5.16 Increases in Low-Density Lipoprotein Cholesterol (LDL-C)~~

~~Increases in LDL-C occur with dapagliflozin [see *Adverse Reactions (6.1)*]. Monitor LDL-C and treat per standard of care after initiating XIGDUO XR.~~

~~5.17 Bladder Cancer~~

~~Across 22 clinical studies, newly diagnosed cases of bladder cancer were reported in 10/6045 patients (0.17%) treated with dapagliflozin and 1/3512 patient (0.03%) treated with placebo/comparator. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 4 cases with dapagliflozin and no cases with placebo/comparator. Bladder cancer risk factors 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 dapagliflozin.~~

~~There are insufficient data to determine whether dapagliflozin has an effect on pre-existing bladder tumors. Consequently, XIGDUO XR 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 XIGDUO XR should be considered.~~

~~5.18 Macrovascular Outcomes~~

~~There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with XIGDUO XR or any other antidiabetic drug.~~

6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

~~• Use in Patients with Renal Impairment [see *Warnings and Precautions (5.3)*]~~
• Lactic Acidosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
• Hypotension [see *Warnings and Precautions (5.~~4~~2)*]
• Ketoacidosis [*see Warnings and Precautions (5.~~5~~3)*]
• Acute Kidney Injury *[see Warnings and Precautions (5.4)]*
•
• Urosepsis and Pyelonephritis [*see Warnings and Precautions (5.~~6~~5)*]
• Use with Medications Known to Cause Hypoglycemia [see *Warnings and Precautions (5.~~11~~6)*]
• Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) *[see Warnings and Precautions (5.7)]*

• Vitamin B_{12} Concentrations [see *Warnings and Precautions (5.~~14~~8)*]
• Genital Mycotic Infections [see *Warnings and Precautions (5.~~15~~9)*]

~~Increases in Low-Density Lipoprotein Cholesterol (LDL-C) [see *Warnings and Precautions (5.16)*] • Bladder Cancer [see *Warnings and Precautions (5.17)*]~~

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 ~~Study~~ 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 m^2	n=41	n=43	n=35	n=141	n=134
Patients (%) with at least one event	2 (4.9%)	3 (7.0%)	4 (11.4%)	27 (19.1%)	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.

~~The~~ In the pool of 12 clinical studies, a subgroup analysis assessed the ~~safety of dapagliflozin was evaluated in a study of~~ patients with ~~moderate renal impairment~~ (eGFR between 30 to less than 60 mL/min/1.73 m^2). ~~In this study~~ 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.

6.2 Postmarketing Experience

Dapagliflozin

Additional adverse reactions have been identified during postapproval use of dapagliflozin. 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.

- Ketoacidosis ~~[see *Warnings and Precautions (5.5)*]~~
  - Acute Kidney Injury and Impairment in Renal Function
-
- Urosepsis and Pyelonephritis ~~[see *Warnings and Precautions (5.6)*]~~
  - Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
  - Rash

Metformin hydrochloride

  - Cholestatic, hepatocellular, and mixed hepatocellular liver injury

7 DRUG INTERACTIONS

7.3 ~~Cationic Drugs~~ Carbonic Anhydrase Inhibitors

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. Consider more frequent monitoring of these patients.

7.4 Drugs that Reduce Metformin ~~hydrochloride~~ Clearance

~~Cationic drugs (e.g., amiloride, cimetidine, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. A 40% increase in exposure (AUC) of metformin when coadministered with~~

~~cimetidine was observed in normal healthy volunteers. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of XIGDUO XR and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system~~.

~~7.4 Use with Other~~ Concomitant use of drugs that interfere with common renal tubular transport 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 *[see Clinical Pharmacology (12.3)]*. Consider the benefits and risks of concomitant use.

7.5 Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving XIGDUO XR.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

~~Pregnancy Category C~~

~~There are no adequate and well-controlled studies of XIGDUO XR or its individual components in pregnant women.~~
~~Based on results of reproductive and developmental toxicity studies in animals, dapagliflozin, a component of XIGDUO XR, may affect renal development and maturation. In a juvenile rat study, increased incidence and/or severity of renal pelvic and tubular dilatations were evident at the lowest tested dose which was approximately 15 times clinical exposure from a 10 mg dose.~~

~~These outcomes occurred with drug exposures during periods of animal development that correlate with~~ 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 *(see Data)*. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*.

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.

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 *(see Data)*. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*.

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

the late second and third trimesters of human pregnancy. ~~During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. XIGDUO XR should be~~

at all doses tested; the lowest of which provided an exposure 15-times the 10 mg clinical dose *(see Data)*.

The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with a HbA1c greater than 7% and has been reported to be as high as 20 to 25% in women with HbA1c greater than 10%. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Human Data

Published data from post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was

used during pregnancy ~~only if the potential benefit justifies the potential risk to the fetus.~~

However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Dapagliflozin

~~In a juvenile toxicity study, when dapagliflozin was~~ Dapagliflozin dosed directly to ~~young~~ juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, increased kidney weights and increased the incidence of renal pelvic and tubular dilatations ~~were reported~~ at all dose levels. Exposure at the lowest dose tested ~~dose~~ was 15 times the ~~maximum~~ 10mg clinical dose, (based on AUC.) The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the a~~pproximate~~a 1-month recovery period.

In a prenatal and postnatal development study, dapagliflozin was administered to maternal rats ~~were dosed~~ from gestation day 6 through lactation day 21 at doses of 1, 15, or 75 mg/kg/day, and pups were indirectly exposed *in utero* and throughout lactation. Increased incidence or severity of renal pelvic dilatation was observed in ~~adult~~ 21-day old pups offspring of treated dams at 75 mg/kg/day (maternal and pup dapagliflozin exposures were 1415 times and 137 times, respectively, the human values at the 10mg clinical dose, based on AUC). Dose-related reductions in pup body weights were observed at ~~doses ≥1 mg/kg/day (approximately ≥19~~ greated or equal to 29 times the 10mg clinical dose(based on AUC). No adverse effects on developmental endpoints were noted at 1 mg/kg/day, ~~or approximately~~ (19 times the 10mg clinical dose , based on AUC). These outcomes occurred with drug exposure during periods of renal development in rats that corresponds to the late second and third trimester of human development.

In embryo-fetal development studies in rats and rabbits, dapagliflozin was administered ~~for intervals coinciding with~~ throughout organogenesis, corresponding to the first trimester ~~period of organogenesis in humans. No developmental toxicities were observed in rabbits at any dose tested~~ -of human pregnancy~~.~~ In rats, dapagliflozin was neither embryolethal nor teratogenic at doses up to 75 mg/kg/day ~~or~~(1441 times the ~~maximum~~ 10mg clinical dose ~~of 10 mg.~~, based on AUC). Dose related effects on the rat fetus (structural abnormalities and reduced body weight) occurred only. At higher ~~doses in rats, malformations of blood vessels, ribs, vertebrae, manubria, and skeletal variations in fetuses at~~ dosages, equal to or greater than ≥150 mg/kg ~~or~~ 2344 times the 10 mg clinical dose , based on AUC), which were associated with maternal toxicity. No developmental toxicities were observed.

~~*Metformin hydrochloride*~~

~~Metformin was not teratogenic~~ in ~~rats and~~ rabbits at doses up to 180 mg/kg/day (1191-times the 10 mg clinical dose, based on AUC).

Metformin HCl

Metformin HCl did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits up to 600 mg/kg/day~~.~~ during the period of organogenesis. This represents an exposure of about 2 and 6 times ~~the MRHD of~~ a 2000 mg clinical dose based on body surface area ~~comparisons~~ (mg/m^2) for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

~~8.3 Nursing Mothers~~

8.2 Lactation

Risk Summary

~~It~~ there ~~is not known whether~~ no information regarding the presence of XIGDUO XR ~~is excreted~~ or dapaglifozin in human milk. ~~In~~ the effects on the breastfed infant, or the effects on milk production.

Limited published studies ~~performed with the individual components, both dapagliflozin (reaching levels 0.49 times~~ report that ~~found in maternal plasma) and~~ metformin ~~are excreted~~ is present in human milk *(see Data)*. However, there is insufficient information on the effects of metformin on the breastfed

infant and no available information on the effects of metformin on milk production. Dapagliflozin is present in the milk of lactating rats.

(see Data). However, due to species specific differences in lactation physiology, the clinical relevance of these data are not clear. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in breastfed infants, advise women that use of XIGDUO XR is not recommended while breastfeeding

Data in juvenile

Dapagliflozin

Dapagliflozin was present in rat milk at a milk/plasma ratio of 0.49 indicating that dapagliflozin and its metabolites are transferred into milk at a concentration that is approximately 50% of that in maternal plasma. Juvenile

rats directly exposed to dapagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs in utero and in the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from dapagliflozin, a decision should be made whether to discontinue nursing or to discontinue XIGDUO XR, taking into account the importance of the drug to the mother.

Metformin hydrochloride

Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

8.3 Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

8.5 Geriatric Use

XIGDUO XR

8.6 Patients with Mild Renal Impairment

(eGFR ≥60 to <90 mL/min/1.73 m^2) *Dapagliflozin*

The pool of 21 double-blind, active- and placebo-controlled

Dapagliflozin

In clinical ~~safety and efficacy~~ studies (dapagliflozin ~~as monotherapy or~~ was associated with increases in ~~combination with other antidiabetic therapies) included 53% (4906/9339) of~~ serum creatinine and decreases in eGFR *[see Adverse Reactions (6.1)]*. Use of dapagliflozin is not recommended when eGFR is less than 45 mL/min/1.73 m^2 *[see Dosage and Administration (2.3), Warnings and Precautions (5.4), and Adverse Reactions (6.1)]* and is contraindicated in patients with ~~mild~~ renal impairment. ~~The safety profile in~~ (eGFR less than 30 mL/min/1.73 m^2) or ESRD *[see Contraindications (4)]*.

patients with ~~mild~~ moderate renal impairment ~~is~~ (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 ~~that in~~ the ~~ov~~general~~l~~ 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.

Metformin hydrochloride

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. XIGDUO XR is contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2 *[see Dosage and Administration (2.3), Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.2)]*.

8.7 Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. XIGDUO XR is not recommended in patients with hepatic impairment *[see Warnings and Precautions (5.1)]*.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Specific Populations

Renal Impairment

~~*XIGDUO XR*~~

~~Use of metformin in patients with renal impairment increases the risk for lactic acidosis. Because XIGDUO XR contains metformin, XIGDUO XR is contraindicated in patients with moderate to severe renal impairment [see *Contraindications (4)* and *Warnings and Precautions (5.3)*]. No dose adjustment of XIGDUO XR is required in patients with mild renal impairment [see *Use in Specific Populations (8.6)*].~~

14.4 Use in Patients with Type 2 Diabetes and Moderate Renal Impairment

Dapagliflozin was assessed in two placebo-controlled studies of patients with type 2 diabetes and moderate renal impairment.

Patients with type 2 diabetes and an eGFR between 45 to less than 60 mL/min/1.73 m^2 inadequately controlled on current diabetes therapy participated in a 24-week, double-blind, placebo-controlled

clinical study (NCT02413398). Patients were randomized to either dapagliflozin 10 mg or placebo, administered orally once daily. At Week 24, dapagliflozin provided statistically significant reductions in HbA1c compared with placebo (Table 15).

Table 15: Results at Week 24 of Placebo-Controlled Study for Dapagliflozin in Patients with Type 2 Diabetes and Renal Impairment (eGFR 45 to less than 60 mL/min/1.73 m^2)

	Dapagliflozin 10 mg	Placebo
Number of patients:	**N=160**	**N=161**
HbA1c (%)		
Baseline (mean)	8.3	8.0
Change from baseline (adjusted mean*)	-0.4†	-0.1
Difference from placebo (adjusted mean*) (95% CI)	-0.3† (-0.5, - 0.1)	

* Least squares mean adjusted for baseline value; at Week 24, HbA1c was missing for 5.6% and 6.8% of individuals treated with dapagliflozin and placebo, respectively. Retrieved dropouts, i.e. observed HbA1c at Week 24 from subjects who discontinued treatment, were used to impute missing values in HbA1c.

† p-value <0.001 versus placebo

העדכונים המהותיים בעלון לצרכן הם:

. לפני שימוש בתרופה

- מחלת הסוכרת שלך אינה בשליטה עם, למשל, היפרגליקמיה חמורה (רמות גבוהות של גלוקוז בדם), בחילות, הקאות, ירידה מהירה במשקל, חמצת לקטית או קטואצידוזיס. קטואצידוזיס הינו מצב קטונים מצטברים בדם מה שעלול להוביל לסכרת לפני תרדמת. הסימפטומים כוללים- כאבי בטן, נשימות מהירות ועמוקות, ישנוניות או הנשימה מתחילה לקבל ריח "פרותי" חריג.

אזהרות מיוחדות הנוגעות בשימוש 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 מהסימנים הבאים, שיכול להיות סימן לחמצת לקטית:

- תחושת קור בכפות ידיים ורגליים

תופעות לוואי

תופעות המחייבות התייחסות מיוחדת: פנה לרופא מיד אם הופיעו התופעות הבאות:

- המרכיב הפעיל מטפורמין בקסיגדו XR עלול לגרום לתופעת לוואי נדירה (עלולה להשפיע על 1 מתוך 10,000 משתמשים) אבל חמורה הנקראת חמצת לקטית, ראה לעיל סעיף **אזהרות מיוחדות הנוגעות בשימוש בקסיגדו XR חמצת לקטית (Lactic Acidosis)**. במקרה ותופעת לוואי זאת מופיעה יש להפסיק מייד שימוש בתכשיר וליצור קשר מייד עם הרופא או עם בית החולים הקרוב ביותר, כיוון שחמצת לקטית עלולה להוביל לתרדמת.
- תופעות לוואי נוספות:
- שוחח עם הרופא שלך מה ניתן לעשות על מנת למנוע התייבשות, כולל כמה נוזלים לשתות מידי יום.

- בעיות בכליה

פגיעה כלייתית פתאומית ארעה למטופלים שנטלו קסיגדו XR . פנה לרופא המטפל מייד אם:

- כמות המזון והשתייה שאתה צורך יורדת, אם אתה חולה ולא יכול לאכול או
- אם אתה מתחיל לאבד נוזלי גוף למשל, כתוצאה מהקאה, משלשול או משהות ממושכת מדי בשמש.

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

זיהום חמור ברקמות הרכות באברי המין או באזור בין איבר המין ופי הטבעת, תופעה נדירה מאד.

- יש לפנות לעזרה רפואית מידית במקרה של התסמינים הבאים: אודם, רגישות או נפיחות באיזור הגנטילי עד פי הטבעת וחום מעל 38^0C או הרגשה כללית רעה.
- תסמינים אלו עלולים להידרדר במהירות ולכן חשוב לפנות לעזרה רפואית במהירות.

תופעות הלוואי השכיחות ביותר בעת נטילת קסיגדו XR:

- זיהום פטרייתי בנרתיק או בפין
- גודש באף או נזלת וכאב גרון
- שלשול
- זיהום בדרכי השתן
- כאב ראש

מקרא לעדכונים המסומנים

הוספת טקסט מהותי מסומנת בצבע. מחיקת טקסט מסומנת בקו חוצה

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

בכבוד רב,
קארין קנבל דובסון

רוקחת ממונה

אסטרהזניקה (ישראל) בע"מ

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