הודעה על החמרה (מידע בטיחות) בעלון לרופא

תאריך:	**25.07.2017**	
שם תכשיר ומספר רישום:	Jardiance Duo 5mg/850 mg:	155-26-34512-00
	Jardiance Duo 5mg/1000 mg:	155-28-34533-00
	Jardiance Duo 12.5mg/850 mg:	155-29-34534-00
	Jardiance Duo 12.5mg/1000 mg:	155-27-34532-00
שם בעל רישום:	**בורינגר אינגלהיים ישראל בע"מ**	

טופס זה מיועד לפרוט ההחמרות בלבד!

עלון לרופא

ההחמרות המבוקשות

פרק בעלון	טקסט נוכחי	טקסט חדש
Black box warning: Risk of lactic acidosis	Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure. The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. If acidosis is suspected, JARDIANCE DUO should be discontinued and the patient hospitalized immediately *[see Warnings and Precautions (5.1)].*	Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL *[see Warnings and Precautions (8.1)]*. Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information *[see Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (8.1), Drug Interactions (10.2), and Use in Specific Populations (11.6, 11.7)]*. (new wording, no new information)

• JARDIANCE DUO is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m^2 *[see Contraindications (7) and Warnings and Precautions (8.1, 8.4)]*. (new wording, no new population)	Do not initiate or continue JARDIANCE DUO in patients with serum creatinine levels greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females. In patients eligible for JARDIANCE DUO based on creatinine cutoff criteria do not initiate or continue JARDIANCE DUO if eGFR is persistently less than 45 mL/min/1.73 m^2. In patients eligible for JARDIANCE DUO based on creatinine cutoff criteria, no dose adjustment is needed if eGFR is greater than or equal to 45 mL/min/1.73 m^2 *[see Contraindications (4) and Warnings and Precautions (5.4)]*.	Dosage & Administration: renal impairment
Discontinue JARDIANCE DUO at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart JARDIANCE DUO if renal function is stable *[see Warnings and Precautions (8.1)]*.	none	Dosage & Administration Discontinuation for Iodinated Contrast Imaging Procedures
There have been postmarketing cases of metformin-associated lactic acidosis, including fatal cases. 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 postmarketing 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 *[see Clinical Pharmacology (12.3)]*. • Before initiating JARDIANCE DUO, obtain an estimated glomerular filtration rate (eGFR). • JARDIANCE DUO is contraindicated in patients with an eGFR below 45 mL/min/1.73 m^2. • Obtain an eGFR at least annually in all patients taking JARDIANCE DUO. 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 JARDIANCE DUO 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 *[see Drug Interactions (10.2)]*. Therefore, consider more frequent monitoring of	Lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during treatment with JARDIANCE DUO and 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 lactic acidosis, metformin plasma levels of >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin is approximately 0.03 cases/1000 patient-years, (with approximately 0.015 fatal 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 impairment, 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, particularly when accompanied by hypoperfusion and hypoxemia due to unstable or acute failure, are at increased risk of lactic acidosis. The risk of lactic acidosis	Warning & Precautions: Lactic Acidosis

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 *[see Use in Specific Populations 11.5)]*. *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 JARDIANCE DUO at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m^2; 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 JARDIANCE DUO 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. JARDIANCE DUO should be temporarily discontinued while patients have restricted food and fluid intake. *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 myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue JARDIANCE DUO. *Excessive Alcohol Intake:* Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving JARDIANCE DUO. *Hepatic Impairment:* Patients with hepatic impairment have developed cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of JARDIANCE DUO in patients with clinical or laboratory evidence of hepatic disease.	increases with the degree of renal impairment 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. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in any patient unless measurement of creatinine clearance demonstrates that renal function is not reduced. 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 be avoided in patients with clinical or laboratory evidence of hepatic impairment. Patients should be cautioned against excessive alcohol intake when taking metformin, since alcohol potentiates the effects of metformin on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure necessitating restricted intake of food or fluids. Use of topiramate, a carbonic anhydrase inhibitor, in epilepsy and migraine prophylaxis may cause dose-dependent metabolic acidosis and may exacerbate the risk of metformin-induced lactic acidosis *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*. The onset of lactic acidosis is often subtle, and accompanied by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. More severe acidosis may be associated with signs such as hypothermia, hypotension, and resistant bradyarrhythmias. Patients should be educated to recognize and promptly report these symptoms. If present, JARDIANCE DUO should be discontinued until lactic acidosis is ruled out. Gastrointestinal symptoms, which are commonly reported during initiation of metformin therapy are less frequently observed in subjects on a chronic, stable, dose of metformin. Gastrointestinal symptoms in subjects on chronic, stable, dose of metformin could be caused by lactic acidosis or other serious disease. To rule out lactic acidosis, serum electrolytes, ketones, blood glucose, blood pH, lactate levels, and blood metformin levels may be useful. Levels of fasting venous plasma lactate above the upper limit of normal but less than 5	

	mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be due to other mechanisms, such as poorly-controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia). Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and supportive measures promptly instituted. Metformin is dialyzable (clearance of up to 170 mL/min under good hemodynamic conditions) and prompt hemodialysis is recommended to remove the accumulated metformin and correct the metabolic acidosis. Such management often results in prompt reversal of symptoms and recovery *[see Boxed Warning and Contraindications (4)]*.	
… Fatal cases of ketoacidosis have been reported in patients taking empagliflozin. JARDIANCE DUO is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (4)]*.	Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including empagliflozin. JARDIANCE DUO is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1)]*.	Warning & Precautions: Ketoacidosis
Empagliflozin causes intravascular volume contraction *[see Warnings and Precautions (8.2)]* and can cause renal impairment *[see Adverse Reactions (9.1)]*. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors, including empagliflozin; some reports involved patients younger than 65 years of age. Before initiating JARDIANCE DUO, 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 JARDIANCE DUO in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue JARDIANCE DUO promptly and institute treatment. Empagliflozin increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. renal	Empagliflozin increases serum creatinine and decreases eGFR *[see Adverse Reactions (6.1)]*. The risk of impaired renal function with empagliflozin is increased in elderly patients and patients with moderate renal impairment. Metformin is known to be substantially excreted by the kidney. The risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Therefore, JARDIANCE DUO is contraindicated in patients with renal impairment (serum creatinine levels greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females, or eGFR less than 45 mL/min/1.73 m^2) *[see Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.6)]*. Before initiation of therapy with JARDIANCE DUO and at least annually thereafter, renal function should be assessed and verified to be normal. In patients in whom development of renal impairment is anticipated (e.g., elderly),	Warning & Precautions: Acute Kidney Injury and Impairment in Renal Function

function abnormalities can occur after initiating JARDIANCE DUO *[see Adverse Reactions (9.1)]*. Renal function should be evaluated prior to initiation of JARDIANCE DUO and monitored periodically thereafter. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2. Use of JARDIANCE DUO is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m^2 *[see Dosage and Administration (5.2), Contraindications (7), Use in Specific Populations (11.6)]*.	renal function should be assessed more frequently and JARDIANCE DUO discontinued if evidence of renal impairment is present (serum creatinine levels greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females, or eGFR less than 45 mL/min/1.73 m^2). *Use of concomitant medications that may affect renal function or metformin disposition:* Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or interfere with the disposition of metformin should be used with caution *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*. *Radiological studies and surgical procedures:* Radiologic studies involving the use of intravascular iodinated contrast materials (e.g., intravenous urogram, intravenous cholangiography, angiography, and computed tomography) 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, JARDIANCE DUO 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 confirmed to be normal. JARDIANCE DUO should be temporarily discontinued 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.	
The following important adverse reactions are described below and elsewhere in the labeling: • Acute Kidney Injury and Impairment in Renal Function *[see Warnings and Precautions (8.4)]*	The following important adverse reactions are described below and elsewhere in the labeling: • Impairment in Renal Function *[see Warnings and Precautions (5.4)]*	Adverse reaction
Risk Summary Based on animal data showing adverse renal effects, JARDIANCE DUO is not recommended during the second and third trimesters of pregnancy. Limited available data with JARDIANCE DUO or empagliflozin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and 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	*Pregnancy Category C* *JARDIANCE DUO* There are no adequate and well-controlled studies in pregnant women with JARDIANCE DUO or its individual components. JARDIANCE DUO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal Data An embryo-fetal development study in pregnant rats did not indicate a teratogenic effect attributed to the	Pregnancy

associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*.

In animal studies, adverse renal changes were observed in rats when empagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 13-times the maximum clinical dose caused renal pelvic and tubule dilatations that were reversible. *Empagliflozin* was not teratogenic in rats and rabbits up to 300 mg/kg/day, which approximates 48-times and 128-times, respectively, the maximum clinical dose of 25 mg when administered during organogenesis. No adverse developmental effects were observed when metformin was administered to pregnant Sprague Dawley rats and rabbits during the period of organogenesis at doses up to 2- and 6-times, respectively, a 2000 mg clinical dose, based on body surface area *(see Data)*.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with HbA1c >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 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk: Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, 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. 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

Empagliflozin: Empagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 10, 30 and 100 mg/kg/day caused increased kidney weights and renal tubular and pelvic dilatation at 100 mg/kg/day, which approximates 13-times the maximum clinical dose of 25 mg, based on AUC. These findings were not observed after a 13 week drug-free recovery period. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal

coadministration of empagliflozin and metformin at exposures of approximately 35- and 14-times the clinical AUC exposure of empagliflozin associated with the 10 mg and 25 mg doses, respectively; and 4-times the clinical AUC exposure of metformin associated with the 2000 mg dose.

Empagliflozin

Based on results from animal studies, empagliflozin may affect renal development and maturation. In studies conducted in rats, empagliflozin crosses the placenta and reaches fetal tissues. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters.

Empagliflozin was not teratogenic in embryo-fetal development studies in rats and rabbits up to 300 mg/kg/day, which approximates 48-times and 128-times, respectively, the maximum clinical dose of 25 mg. At higher doses, causing maternal toxicity, malformations of limb bones increased in fetuses at 700 mg/kg/day or 154 times the 25 mg maximum clinical dose in rats. In the rabbit, higher doses of empagliflozin resulted in maternal and fetal toxicity at 700 mg/kg/day, or 139 times the 25 mg maximum clinical dose.

In pre- and postnatal development studies in pregnant rats, empagliflozin was administered from gestation day 6 through to lactation day 20 (weaning) at up to 100 mg/kg/day (approximately 16 times the 25 mg maximum clinical dose) without maternal toxicity. Reduced body weight was observed in the offspring at greater than or equal to 30 mg/kg/day (approximately 4 times the 25 mg maximum clinical dose).

Metformin hydrochloride

Metformin has been studied for embryo-fetal effects in 2 rat strains and in rabbits. Metformin was not teratogenic in Sprague Dawley rats up to 600 mg/kg or in Wistar Han rats up to 200 mg/kg (2-3 times the clinical dose based on body surface area or exposure, respectively). At higher maternally toxic doses (9 and 23 times the clinical dose based on exposure), an increased incidence of rib and scapula skeletal malformations was observed in the Wistar Han strain. Metformin was not teratogenic in rabbits at doses up to 140 mg/kg (similar to clinical dose based on body surface area).

Metformin administered to female Sprague Dawley rats from gestation day 6 to lactation day 21 up to 600 mg/kg/day (2 times the maximum clinical

development.	dose based on body surface area) had no effect on prenatal or postnatal development of offspring. Metformin crosses the placenta into the fetus in rats and humans.	
Risk Summary There is no information regarding the presence of JARDIANCE DUO or empagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that metformin 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. Empagliflozin is present in the milk of lactating rats *(see Data)*. 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 a breastfed infant, advise women that use of JARDIANCE DUO is not recommended while breastfeeding. *Data* 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. Empagliflozin was present at a low level in rat fetal tissues after a single oral dose to the dams at gestation day 18. In rat milk, the mean milk to plasma ratio ranged from 0.634 -5, and was greater than one from 2 to 24 hours post-dose. The mean maximal milk to plasma ratio of 5 occurred at 8 hours post-dose, suggesting accumulation of empagliflozin in the milk. Juvenile rats directly exposed to empagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.	No studies in lactating animals have been conducted with the combined components of JARDIANCE DUO. In studies performed with the individual components, both empagliflozin and metformin were secreted in the milk of lactating rats. It is not known whether empagliflozin is excreted in human milk. Metformin is excreted in human milk in low concentrations. Because many drugs are excreted in human milk and because the potential for serious adverse reactions in nursing infants may exist from JARDIANCE DUO, a decision should be made whether to discontinue nursing or to discontinue JARDIANCE DUO, taking into account the importance of the drug to the mother. *Empagliflozin* Empagliflozin is secreted in the milk of lactating rats reaching levels up to 5 times higher than that in maternal plasma. 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. *Metformin hydrochloride* Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers.	Lactation
11.3 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.	none	Females and Males of Reproductive Potential
Metformin hydrochloride Controlled clinical studies of metformin hydrochloride did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. In general, dose selection for an elderly patient should be cautious,	*Metformin hydrochloride* Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. The initial and	Geriatric use

usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients *[see Contraindications (7), Warnings and Precautions (8.1), and Clinical Pharmacology (15.3)].*	maintenance dosing of metformin should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dose adjustment should be based on a careful assessment of renal function *[see Contraindications (4), Warnings and Precautions (5.4), and Clinical Pharmacology (12.3)].*	

עלון לצרכן

ההחמרות המבוקשות		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**
אזהרות מיוחדות הנוגעות לשימוש התרופה	הסיכון גבוה יותר לפתח חמצת לקטית עם ג'ארדיאנס דואו אם הנך: ....בן 80 ומעלה ולא עברת בדיקות תפקודי כלייה	הסיכון גבוה יותר לפתח חמצת לקטית עם ג'ארדיאנס דואו אם הנך: ....בן 65 ומעלה מאחר ובגילאים אלו עלולות להיות בעיות בתפקודי הכלייה, כבד או לב. עלייך להקפיד על בדיקות תפקודי כלייה תכופים.
תגובות בין תרופתיות	**תרופות קטיוניות** (כגון, אמילוריד, דיגוקסין, מורפין, פרוקאינאמיד, קווינידין, קווינין, רניטידין, טריאמטרן, טרימטופרים, וונקומיצין, סימטידין) – עלול להוריד את יעילות התכשיר וייתכן ויהיה צורך בהתאמת מינון של תרופות אלו או של ג'ארדיאנס דואו.	•**תרופות המפחיתות את הפינוי של מטפורמין** (כגון, רנולאזין, ונדטניב, דולוטגרביר) עלולות להעלות את רמות המטפורמין בדם והלגביר את הסיכון לחמצת לקטית – יתכן והרופא ישקול את הטיפול המתאים.
הריון והנקה	אם את בהריון, מתכננת הריון, מניקה או מתכננת הנקה יש להיוועץ ברופא לפני השימוש בתרופה. אין מידע לגבי השפעת התרופה על העובר. אם את בהריון, שוחחי עם הרופא שלך בנוגע לדרך הטובה ביותר לשלוט ברמות הסוכר בדם בזמן ההריון. אין להשתמש בג'ארדיאנס דואו אם הינך בהריון. אין מידע לגבי השפעת התרופה על העובר. אין להשתמש בג'ארדיאנס דואו אם הינך מניקה. אין מידע לגבי מעבר התרופה לחלב האם.	אם את בהריון, מתכננת הריון, מניקה או מתכננת הנקה יש להיוועץ ברופא לפני השימוש בתרופה. אין להשתמש בג'ארדיאנס דואו בהיריון, התכשיר עלול להזיק לעוברך.. אם את בהריון, שוחחי עם הרופא שלך בנוגע לדרך הטובה ביותר לשלוט ברמות הסוכר בדם בזמן ההריון. אם הנך מניקה, אין להשתמש בג'ארדיאנס דואו.. - היוועצי ברופא שלך לגבי הדרך הטובה ביותר להאכיל את תינוקך במידה ואת נוטלת ג'ארדיאנס דואו. פוריות בקרב נשים אם הנך אישה בגיל הפרהמנופאוזה (טרם הפסקת הווסת), אשר הווסת אינה מופיעה באופן סדיר או לא מויעה כלל, התייעצי עם הרופא המטפל לגבי אמצעי מניעה בזמן הטיפול בג'ארדיאנס דואו, אם אינך מעוניינת להיכנס להיריון, מאחר וג'ארדיאנס דואו עלול להגביר את הסיכויים להיכנס להיריון.
תופעות לוואי	**בעיות בכליה** - בייחוד במטופלים בגיל 75 ומעלה או באנשים עם בעיות כליה קיימות.	בעיות בכליות פגיעה כלייתית פתאומית התרחשה באנשים שטופלו בג'ארדיאנס דואו. דווח לרופא מייד אם הנך: • מפחית את כמות המזון או הנוזלים שהנך שותה, למשל אם הנך חולה או לא יכול לאכול, או • מאבד נוזלים מהגופך, למשל, בעקבות

		הקאות, שלשול או בעקבות שהייה ממושכת בשמש.