יולי 2020

רופא/ה נכבד/ה
רוקח/ת נכבד/ה

הנדון: JANUET® 50 mg/500 mg, 50 mg/850 mg, 50 mg/1000 mg
ג'נואט® 50 מ"ג/500 מ"ג, 50 מ"ג/850 מ"ג, 50 מ"ג/1000 מ"ג

Dosage Form: Tablets
Composition: Sitagliptin (as monohydrate phosphate) and metformin Hydrochloride.

חברת מרק שארפ ודוהם ישראל (MSD) מבקשת ליידע על עדכון העלונים לרופא ולצרכן של ג'נואט.

להלן לשון ההתוויה המאושרת לתכשיר:
JANUET is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus.

למידע מלא ולהוראות מתן מפורטות, יש לעיין בעלון לרופא המאושר על ידי משרד הבריאות.

עדכונים מהותיים בעלון לרופא:
טקסט מהותי שהתווסף מודגש בקו תחתון טקסט שנמחק מופיע עם קו חוצה.

WARNING: LACTIC ACIDOSIS

~~**Lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal 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, JANUET 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 (5.1)].

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrae 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 (5.1), Drug Interactions (7), and Use in Specific Populations (8.6, 8.7)].

If metformin-associated lactic acidosis is suspected, immediately discontinue JANUET and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended [see Warnings and Precautions (5.1)].

2.2 Recommendations for Use in Renal Impairment
An eGFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.
The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis [see Warnings and Precautions (5.1)] should be reviewed before considering initiation of metformin in patients with eGFR<60 mL/min/1.73 m2.
If no adequate strength of JANUET is available, individual monocomponents should be used instead of the fixed dose combination.

eGFR mL/min/1.73 m^2	Metformin	Sitagliptin
60-89	Maximum daily dose is 2550 mg. Dose reduction may be considered in relation to declining renal function.	Maximum daily dose is 100 mg.
45-59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 100 mg.
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 50 mg.
< 30	Metformin is contraindicated.	Maximum daily dose is 25 mg.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

~~*Metformin hydrochloride*~~

~~Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with JANUET; 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 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 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, 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. 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, either acute or chronic, 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 (5.4, 5.6, 5.7, 5.11)]*.~~

~~The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated 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 (5.12)]*. 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.~~

~~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 explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling *[see Warnings and Precautions (5.8, 5.13)]*.~~

~~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 general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery *[see Contraindications (4); Warnings and Precautions (5.6, 5.7, 5.10, 5.11, 5.12)]*.~~

There have been postmarketing 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 (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate/pyruvate ratio; metformin plasma levels were 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 JANUET. In JANUET-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (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.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue JANUET 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 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 Dosage and Administration (2.2), Clinical Pharmacology (12.3)]*.

- Before initiating JANUET, obtain an estimated glomerular filtration rate (eGFR).
- JANUET is contraindicated in patients with an eGFR below 30 mL/min/1.73 m^2 *[see Contraindications (4).*

- JANUET is not recommended in patients with an eGFR between 30 and less than 45 mL/min/1.73 m^2 because these patients require a lower dosage of sitagliptin than what is available in the fixed combination JANUET product.
- Obtain an eGFR at least annually in all patients taking JANUET. 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 JANUET 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 (7)].* 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 [*see Use in Specific Populations (8.5)].*

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 JANUET at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 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 JANUET 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. JANUET 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 JANUET.

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 JANUET.

Hepatic Impairment

Patients with hepatic impairment have developed with cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of JANUET in patients with clinical or laboratory evidence of hepatic disease.

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5.3 Heart Failure

An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

Consider the risks and benefits of JANUET prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of JANUET.

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5.5 Vitamin B_{12} ~~Levels~~ *Deficiency*

… Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels.

~~Certain individuals (those with inadequate Vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B_{12} levels. In these patients, routine serum Vitamin B_{12} measurements at two- to three-year intervals may be useful.~~

…

5.11 Bullous Pemphigoid

Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving JANUET. If bullous pemphigoid is suspected, JANUET should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

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7 DRUG INTERACTIONS…

~~**7.2 Cationic Drugs**~~

~~Cationic drugs (e.g., amiloride, 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. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of JANUET and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.~~

7.2 Drugs that Reduce Metformin Clearance

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.

7.3 Alcohol

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

7.4 Insulin Secretagogues or Insulin

Co-administration of JANUET with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia. (See Warnings and Precautions (5.7).)

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7.6 Digoxin

There was a slight increase in the area under the curve (AUC 11%) and mean peak drug concentration (C_{max} 18%) of digoxin with the coadministration of 100 mg sitagliptin for 10 days. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or JANUET is recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

~~*Pregnancy Category B:*~~

~~*JANUET*~~

~~There are no adequate and well-controlled studies in pregnant women with JANUET or its individual components; therefore, the safety of JANUET in pregnant women is not known. JANUET should be used during pregnancy only if clearly needed.~~

~~No animal studies have been conducted with the combined products in JANUET to evaluate effects on reproduction. The following data are based on findings in studies performed with sitagliptin or metformin individually.~~

~~*Sitagliptin*~~

~~Reproduction studies have been performed in rats and rabbits. Doses of sitagliptin up to 125 mg/kg (approximately 12 times the human exposure at the maximum recommended human dose) did not impair fertility or harm the fetus. There are, however, no adequate and well-controlled studies with sitagliptin in pregnant women.~~

~~Sitagliptin administered to pregnant female rats and rabbits from gestation day 6 to 20 (organogenesis) was not teratogenic at oral doses up to 250 mg/kg (rats) and 125 mg/kg (rabbits), or approximately 30 and 20 times human exposure at the maximum recommended~~

~~human dose (MRHD) of 100 mg/day based on AUC comparisons. Higher doses increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100 times human exposure at the MRHD.~~

~~Sitagliptin administered to female rats from gestation day 6 to lactation day 21 decreased body weight in male and female offspring at 1000 mg/kg. No functional or behavioral toxicity was observed in offspring of rats.~~

~~Placental transfer of sitagliptin administered to pregnant rats was approximately 45% at 2 hours and 80% at 24 hours postdose. Placental transfer of sitagliptin administered to pregnant rabbits was approximately 66% at 2 hours and 30% at 24 hours.~~

~~*Metformin hydrochloride*~~

~~Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2,000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.~~

~~8.3 Nursing Mothers~~

~~No studies in lactating animals have been conducted with the combined components of JANUET. In studies performed with the individual components, both sitagliptin and metformin are secreted in the milk of lactating rats. It is not known whether sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when JANUET is administered to a nursing woman.~~

Risk Summary

The limited available data with JANUET in pregnant women are not sufficient to inform 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 associated with poorly controlled diabetes in pregnancy [see Clinical Considerations]. No adverse developmental effects were observed when sitagliptin was administered to pregnant rats and rabbits during organogenesis at oral doses up to 30-times and 20-times, respectively, the 100 mg clinical dose, based on AUC. No adverse developmental effects were observed when metformin was administered to pregnant Sprague Dawley rats and rabbits during 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 Hemoglobin A1c>7% and has been reported to be as high as 20-25% in women with a Hemoglobin A1c>10%.

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, 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 do not report a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin is used during pregnancy. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Sitagliptin and Metformin

No animal reproduction studies were conducted with the coadministration of sitagliptin and metformin.

Sitagliptin

In embryo-fetal development studies, sitagliptin administered to pregnant rats and rabbits during organogenesis (gestation day 6 to 20) did not adversely affect developmental outcomes at oral doses up to 250 mg/kg (30-times the 100 mg clinical doses) and 125 mg/kg (20-times the 100 mg clinical dose), respectively, based on AUC. Higher doses in rats associated with maternal toxicity increased the incidence of rib malformations in offspring at 1000- mg/kg, or approximately 100- times the clinical dose, based on AUC. Placental transfer of sitagliptin was observed in pregnant rats and rabbits.

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 caused no functional or behavioral toxicity in offspring of rats at doses up to 1000 mg/kg

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 a 2000 mg clinical dose based on body surface area (mg/m^2) for rats and rabbits, respectively.

8.2 Lactation

Risk Summary

JANUET

There is no information regarding the presence of JANUET 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]. There are no reports of adverse effects on breastfed infants exposed to metformin. There is no information on the effects of metformin on milk production. Sitagliptin is present in rat milk, and therefore possibly present in human milk [see Data]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for JANUET, and any potential adverse effects on the breastfed infant from JANUET or from the underlying maternal condition.

Data

Sitagliptin

Sitagliptin is secreted in the milk of lactating rats at a milk to plasma ration of 4:1.

Metformin HCl

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.

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8.5 Geriatric Use

JANUET

Because sitagliptin and metformin are substantially excreted by the kidney, and because aging can be associated with reduced renal function, renal function should be assessed more frequently in elderly patients. *[See Warnings and Precautions (5.1, 5.4); Clinical Pharmacology (12.3).]*

Sitagliptin

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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. In general, dose selection for an elderly patient should be cautious, 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 (4); Warnings and Precautions (5.1); Clinical Pharmacology (12.3).]*

8.6 Renal Impairment

JANUET

JANUET is not recommended in patients with an eGFR between 30 and less than 45 mL/min/1.73 m^2 because these patients require a lower dosage of sitagliptin than what is available in the fixed dose combination JANUET product. JANUET is contraindicated in severe renal impairment, patients with an eGFR below 30 mL/min/1.73 m². *[See Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3).]*

Sitagliptin

Sitagliptin is excreted by the kidney, and sitagliptin exposure is increased in patients with renal impairment. Lower dosages are recommended in patients with eGFR less than 45 mL/min/1.73 m² (moderate and severe renal impairment, as well as in ESRD patients requiring dialysis).

Metformin HCl

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment.

8.7 Hepatic Impairment

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

עדכונים מהותיים בעלון לצרכן:

טקסט מהותי שהתווסף מודגש בקו תחתון טקסט שנמחק מופיע עם קו חוצה.

2.1 אל תיטול ג'נואט אם:

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- ~~תפקוד הכליות שלך אינו תקין~~. יש לך תפקוד כלייתי ירוד באופן חמור (הרופא שלך יגדיר מהי רמת הפגיעה בתפקוד הכלייתי שלך)

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- ~~הינך עומד לקבל זריקת צבע או חומרי-ניגוד לצורך צילום רנטגן, יש להפסיק מתן **ג'נואט** לזמן קצר. דבר עם הרופא שלך באשר למועד הפסקת **ג'נואט** ולמועד חידוש המתן (ראה סעיף 3 "איך תשתמש ב**ג'נואט**?").~~

2.2 אזהרות מיוחדות בנוגע לשימוש בג'נואט

לפני נטילת ג'נואט, ספר לרופא שלך אם:

...

- יש לך בעיות חמורות בכליה.

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- ~~גילך עולה על 80 שנים. אם הינך מעל גיל 80 שנים אסור לך ליטול **ג'נואט**, אלא אם כן הכליות שלך נבדקו והן תקינות.~~
- הינך עומד לקבל זריקת צבע או חומרי ניגוד לצורך צילום רנטגן, ייתכן ויהיה צורך להפסיק נטילת **ג'נואט** לזמן קצר. היוועץ ברופא שלך מתי עליך להפסיק ליטול **ג'נואט** ומתי עליך להתחיל ליטול **ג'נואט** שוב. ראה סעיף 4 תופעות לוואי אפשריות.
- ...

2.3 נטילת תרופות אחרות

אם הינך נוטל או נטלת לאחרונה תרופות אחרות, כולל תרופות ללא מרשם רופא ותוספי תזונה, עליך להודיע על כך לרופא המטפל או לרוקח. במיוחד אם אתה לוקח:

- **טופירמט (לטיפול בפרכוסים ומיגרנות)**
- **אצטאזולאמיד (לטיפול בבצקת, גלאוקומה ומחלת ים)**
- **דולוטגראביר (לטיפול בזיהום של HIV)**
- **סימטידין (לטיפול באולקוס)**
- **ראנולזין**
- **ואנדטניב**

4. תופעות לוואי אפשריות

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1. חמצת לקטית.

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דבר עם הרופא שלך מיד, אם יש לך כל אחד מהתסמינים הבאים, ~~הפסק לקחת ג'נואט ודבר עם הרופא שלך מיד אם הינך מפתח אחד מהתסמינים הבאים~~ ,אשר עלולים להיות סימנים של חמצת לקטית (lactic acidosis):

...

- הינך מרגיש קור בידיים או בכפות הרגליים שלך
-

אצל מרבית האנשים שהיתה להם חמצת לקטית עם מטפורמין סובלים מדברים אחרים, אשר בשילוב עם מטפורמין הובילו לחמצת לקטית. ספר לרופא שלך אם יש לך כל אחד מהבאים, מכיוון שיש לך סיכוי גבוה יותר לפתח חמצת לקטית (lactic acidosis) עם **ג'נואט** אם אתה:

- סובל מבעיות חמורות בכליה או שהכליות שלך מושפעות מבדיקות רנטגן מסויימות שנעשה בהן שימוש בחומר צבע בהזרקה. ~~אין ליטול **ג'נואט** אם פעילות הכליות שלך אינה תקינה.~~
- סובל מבעיות בכבד.
- ~~סובל מאי-ספיקת לב הדורשת טיפול תרופתי.~~

...

- ~~עובר בדיקות רנטגן עם חומרי צבע או חומרי-ניגוד המוזרקים לתוך גופך.~~
- עובר ניתוח.
- סובל מהתקף לב, זיהום חמור או שבץ.
- ~~בן 80 שנים ומעלה ולא עברת בדיקות תפקודי כליה.~~

הדרך הטובה ביותר להימנע מבעיה של חמצת לקטית ממטפורמין היא לספר לרופא שלך אם יש לך כל אחת מהבעיות ברשימה למעלה. ייתכן והרופא שלך יחליט להפסיק לך את **ג'נואט** לזמן מה אם יש לך כל אחד מהדברים הללו.

...

3. אי ספיקת לב. אי ספיקת לב פירושו שליבך אינו שואב דם בצורה טובה דיה.
לפני שהינך מתחיל ליטול ג'נואט, ספר לרופא שלך אם אי פעם היה לך אי ספיקת לב או יש לך בעיות עם הכליות שלך.
צור קשר עם הרופא שלך באופן מיידי אם יש לך אחד מהתסמינים הבאים:

- קוצר נשימה מתגבר או בעיה לנשום, במיוחד כאשר אתה דוכב
- נפיחות או אגירת נוזלים, בעיקר ברכפות הרגליים, קרסוליים או רגליים
- עליה מהירה במיוחד במשקל
- עייפות לא רגילה

אלו עלולים להיות תסמינים של אי ספיקת לב

...

8. **תגובות עוריות** (שכיחות אינה ידועה)., חלק מהאנשים הנוטלים תרופות הנקראות מעכבי DPP-4 אחת התרופות בג'נואט, עלולים לפתח תגובה עורית שנקראת bullous pemphigoid שבה יתכן ויהיה צורך בטיפול בבית חולים. ספר לרופא שלך מייד אם אתה מפתח שלפוחיות או פציעה של השכבה החיצונית של העור שלך (שחיקה). ייתכן והרופא שלך יגיד לך להפסיק לקחת ג'נואט.

...

לג'נואט עלולות להיות תופעות לוואי אחרות כולל:

- **נפיחות של הידיים או הרגליים.** נפיחות של הידיים והרגליים עלולה לקרות אם הינך נוטל **ג'נואט** בשילוב עם רוזיגליטאזון (אבנדיה®). רוזיגליטאזון הינה תרופה מסוג אחר לסוכרת.
- ~~עלייה באנזימי כבד~~
- ...
- שלפוחיות

בעלונים לרופא ולצרכן היו עדכונים נוספים שאינם מהותיים ואינם נכללים בהודעה זו.
העלון לרופא והעלון לצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום, חברת MSD, בטלפון 09-9533333.
JANUET® 50 mg/500 mg, 50 mg/850 mg, 50 mg/1000 mg מופצות ע"י חברת נובולוג בע"מ.

בברכה,
מיכל סרפר, רוקחת ממונה
MSD ישראל

References:
Israeli approved PC revised on 7/2020
Israeli approved PPI revised on 7/2020