אוגוסט 2020

רופא/ה נכבד/ה
רוקח/ת נכבד/ה

הנדון: JANUET® XR 50 mg/500 mg, 50 mg/1000 mg, 100 mg/1000 mg Tablets
ג'נואט® XR 50 מ"ג/500 מ"ג, 50 מ"ג/1000 מ"ג, 100 מ"ג/1000 מ"ג טבליות

Dosage Form: Extended release Tablets
Composition: Each tablet contains Sitagliptin (as phosphate salt) and Metformin Hydrochloride (extended release)

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

להלן לשון ההתוויה המאושרת לתכשיר:
Januet XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin extended-release is appropriate.

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 of lactic acidosis 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 XR (sitagliptin and metformin HCl extended-release) tablets 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 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 (5.1), Drug Interactions (7), and Use in Specific Populations (8.6, 8.7)].* If metformin-associated lactic acidosis is suspected, immediately discontinue JANUET XR 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.

4 CONTRAINDICATIONS

JANUET XR is contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2)(~~e.g., serum creatinine levels greater than or equal to 1.5 mg/dL for men, greater than or equal to 1.4 mg/dL for women or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia *[see Warnings and Precautions (5.1)]*.~~
- ~~Hypersensitivity to metformin hydrochloride.~~

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

~~*Metformin hydrochloride*~~

~~Lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during treatment with JANUET XR 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 concentrations (>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 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 JANUET XR. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. JANUET XR treatment should not be initiated in any patient unless measurement of creatinine clearance demonstrates that renal function is not reduced. In addition, JANUET XR 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, JANUET XR should generally be avoided in patients with clinical or laboratory evidence of hepatic impairment. Patients should be cautioned against excessive alcohol intake when taking JANUET XR, because alcohol potentiates the effects of metformin on lactate metabolism. In addition, JANUET XR 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 frequently cause dose-dependent metabolic acidosis (in controlled trials, 32% and 67% for adjunctive treatment in adults and pediatric patients, respectively, and 15 to 25% for monotherapy of epilepsy, with decrease in serum bicarbonate to less than 20 mEq/L; 3% and 11% for adjunctive treatment in adults and pediatric patients, respectively, and 1 to 7% for monotherapy of epilepsy, with decrease in serum bicarbonate to less than 17 mEq/L) and may exacerbate the risk of metformin-induced lactic acidosis. *[See Drug Interactions (7.1); Clinical Pharmacology (12).]* 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.~~

~~Patients should be educated to promptly report these symptoms to their physician should they occur. If present, JANUET XR should be withdrawn until lactic acidosis is ruled out. Serum electrolytes, ketones, blood glucose, blood pH, lactate levels, and blood metformin levels may be useful. Once a patient is stabilized on any dose level of JANUET XR, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to recur. 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 JANUET XR 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. 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 JANUET XR, 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).]*~~

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 XR. In JANUET XR-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin 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 XR and report these symptoms to their health care 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 XR, obtain an estimated glomerular filtration rate (eGFR).
- JANUET XR is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m2. Discontinue JANUET XR if the patient's eGFR later falls below 30 mL/min/1.73 m2 [see Dosage and Administration (2.2) and Contraindications (4)].
- Initiation of JANUET XR is not recommended in patients with eGFR between 30 and 45 mL/min/1.73 m2.
- In patients taking JANUET XR whose eGFR later falls below 45 mL/min/1.73 m2, assess the benefit and risk of continuing therapy
- Obtain an eGFR at least annually in all patients taking JANUET XR. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Drug Interactions

The concomitant use of JANUET XR with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation [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 XR 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 m2; 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 XR if renal function is stable.

Surgery and Other Procedures

Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. JANUET XR 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 XR.

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 XR.

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 XR in patients with clinical or laboratory evidence of hepatic disease.

~~**5.3 Impaired Hepatic Function**~~

~~Since impaired hepatic function has been associated with some cases of lactic acidosis, JANUET XR should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.~~

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 XR 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 XR.

5.4 Assessment of Renal Function

Metformin and sitagliptin are substantially excreted by the kidney.

Metformin HCl

~~The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Therefore~~, JANUET XR is contraindicated in patients with severe renal impairment (see Contraindications (4) and Warnings and Precautions (5.1)).

~~Before initiation of JANUET XR and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated (e.g., elderly), renal function should be assessed more frequently and JANUET XR discontinued if evidence of renal impairment is present.~~

5.5 Vitamin B12 Deficiency

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. Measure hematologic parameters on an annual basis and vitamin B12 measurements at 2- to 3-year intervals in patients on JANUET XR and manage any abnormalities [see Adverse Reactions (6.1)].

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

~~In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on JANUET XR and any apparent abnormalities should be appropriately investigated and managed. *[See Adverse Reactions (6.1).]*~~

~~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.~~

~~**5.6 Alcohol Intake**~~

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

~~**5.7 Surgical Procedures**~~

~~Use of JANUET 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.~~

~~**5.10 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 (7.2)]*, should be used with caution.~~

~~**5.11 Radiologic Studies with Intravascular Iodinated Contrast Materials**~~

~~Intravascular contrast studies with iodinated materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin *[see Contraindications (4)]*. Therefore, in patients in whom any such study is planned, JANUET 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.~~

~~**5.12 Hypoxic States**~~

~~Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on JANUET XR therapy, the drug should be promptly discontinued.~~

5.11 Bullous Pemphigoid

Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPPP-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 XR. If bullous pemphigoid is suspected, JANUET XR should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

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6 ADVERSE REACTIONS

6.2 Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of sitagliptin with metformin, sitagliptin, or metformin. ~~with or without metformin, and/or in combination with other antidiabetic medications.~~

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mouth ulceration; stomatitis; cholestatic, hepatocellular, and mixed hepatocellular liver injury, ; rhabdomyolysis.

7 DRUG INTERACTIONS

7.1 Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with JANUET XR may increase the risk of lactic acidosis. ~~metabolic acidosis. Use these drugs with caution in patients treated with JANUET XR, as the risk of lactic acidosis may increase~~. Consider more frequent monitoring of these patients.

7.2 ~~Cationic Drugs~~ Drugs that Reduce Metformin Clearance

~~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 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.~~ 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 XR.

7.4 Insulin Secretagogues or Insulin

Coadministration of JANUET XR 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).)

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 XR is recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B Exposure Registry:

~~*JANUET XR*~~

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

Risk Summary

The limited available data with JANUET XR 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 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.

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8.2 Lactation

Risk Summary

There is no information regarding the presence of JANUET XR 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 XR, and any potential adverse effects on the breastfed infant from JANUET XR or from the underlying maternal condition.

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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.~~unless clearly needed.~~

~~***8.3 Nursing MothersFemales 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.***~~

~~No studies in lactating animals have been conducted with the combined components of JANUET XR. 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 or metformin are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when JANUET XR is administered to a nursing woman~~.

8.5 Geriatric Use

JANUET XR

Because sitagliptin and metformin are substantially excreted by the kidney, and because aging can be associated with reduced renal function, ~~JANUET XR should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function.~~ renal function should be assessed more frequently in elderly patients.

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Metformin HCl

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. ~~Metformin should only be used in patients with normal renal function~~. 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. ~~The initial and 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~~.

8.6 Renal Impairment

JANUET XR

The dose of the sitagliptin component should be limited to 50 mg once daily if eGFR falls below 45 mL/min/1.73 m².

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

JANUET XR is contraindicated in severe renal impairment, patients with an eGFR below 30 mL/min/1.73 m2. ~~The dose of the sitagliptin component should be limited to 50 mg once daily if the eGFR falls below 45 mL/min/1.73m^2~~

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 XR 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:
...
- יש לך תפקוד כלייתי ירוד באופן חמור (הרופא שלך יגדיר מהי רמת הפגיעה בתפקוד הכלייתי שלך)

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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

3.איך תשתמש בג'נואט XR?
בדיקות ומעקב:
...במידה ויש לך ירידה בתפקודי כליות, ייתכן והרופא ירשום לך מינון נמוך יותר

4. תופעות לוואי אפשריות
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4.1 חמצת לקטית.
מטפורמין, אחת התרופות בג'נואט XR, עלולה לגרום למצב נדיר (יכולה להופיע בעד 1 מתוך 10000 משתמשים) אך חמור הנקרא חמצת לקטית - lactic acidosis (הצטברות של חומצה לקטית בדם), אשר עלולה לגרום למוות. חמצת לקטית הינה מצב חירום רפואי המחייב טיפול בבית חולים.
~~הפסק ליטול ג'נואט XRוצור קשר עם הרופא שלך מיד~~ דבר עם הרופא שלך מיד, אם יש לך כל אחד מהתסמינים הבאים, אשר עלולים להיות סימנים של חמצת לקטית - lactic acidosis:
- הינך מרגיש קור בידיים או בכפות הרגליים שלך
- הינך מרגיש סחרחורת או מסוחרר
- יש לך דופק איטי או לא סדיר
- הינך מרגיש מאד חלש או עייף
- יש לך כאבי שרירים לא רגילים (חריגים)
- יש לך קשיי נשימה
- הינך מרגיש ישנוני או מנומנם
- יש לך כאבים בבטן, בחילות או הקאות
- ~~הינך מרגיש מאד חלש או עייף~~
- ~~יש לך כאבי שרירים לא רגילים (חריגים)~~
- ~~יש לך קשיי נשימה~~
- ~~הינך חש בישנוניות חריגה, או הינך ישן לזמן ארוך יותר מהרגיל~~
- ~~יש לך כאבי בטן פתאומיים או בעיות מעיים פתאומיות המלוות בבחילות והקאות או שלשולים~~
- ~~קר לך, במיוחד בזרועות וברגליים~~
- ~~הינך מרגיש סחרחורת או מסוחרר~~
- ~~יש לך דופק איטי או לא סדיר~~

~~יש לך סיכוי גבוה יותר לפתח חמצת לקטית - lactic acidosis אם אתה:~~
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 (acidosis lactic) עם **ג'נואט XR** אם אתה:

- סובל מבעיות חמורות בכליה או שהכליות שלך מושפעות מבדיקות רנטגן מסויימות שנעשה בהן שימוש בחומר צבע בהזרקה. ~~אין ליטול **ג'נואט XR** 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~~

...

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 ה**ג'נואט XR** לזמן מה אם יש לך כל אחד מהדברים הללו.

...

4.3. אי ספיקת לב. אי ספיקת לב פירושו שליבך אינו שואב דם בצורה טובה דיה.
לפני שהינך מתחיל ליטול ג'נואטXR , 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

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4.8 **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'נואטXR .

...

לג'נואט עלולות להיות תופעות לוואי אחרות כולל:

...

- ~~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® XR 100 mg/1000 mg, 50 mg/1000 mg, 50 mg/500 mg מופצות ע"י חברת נובולוג בע"מ.

בברכה,
מיכל סרפר, רוקחת ממונה
MSD ישראל

References:
Israeli approved PC revised on 8/2020
Israeli approved PPI revised on 8/2020