JANUVIA, JANUMET, JANUMET XR SSI (long) For HCP

Indication:

- **JANUVIA (*sitagliptin phosphate)*** is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus as monotherapy or in combination with metformin, or a PPARγ agonist, or a sulfonylurea, or insulin (with or without metformin), or a sulfonylurea and metformin, or a PPARγ agonist and metformin, when the current regimen, with diet and exercise does not provide adequate glycemic control or due to contraindications or intolerance.

- **JANUMET (*sitagliptin phosphate/metformin HCl*)** and **JANUMET XR (*sitagliptin phosphate/metformin HCl extended release*)** are 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 is appropriate.

Dosing Recommended:

- The recommended dose of **JANUVIA** is 100 mg once daily as monotherapy or as combination therapies. JANUVIA can be taken with or without food. When JANUVIA is used in combination with a sulfonylurea or with insulin, a lower dose of sulfonylurea or insulin may be considered.

- The dosage of **JANUMET** and **JANUMET XR** should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability not exceeding the maximum recommended daily dose of 100mg sitagliptin and 2000mg metformin.

- **JANUMET** should be generally given twice daily with meals, with gradual dose escalation. Patients may be titrated up to 50 mg sitagliptin/1000 mg metformin hydrochloride twice daily.

- **JANUMET XR** should be generally taken as a single tablet once daily with a meal preferably in the evening. Patients using two JANUMET XR tablets (such as two 50 mg sitagliptin/500 mg metformin hydrochloride ER tablets or two 50 mg sitagliptin/1000 mg metformin hydrochloride ER tablets) should take the two tablets together once daily. JANUMET XR should be swallowed whole, it must not be split, crushed, or chewed.

- **JANUVIA, JANUMET and JANUMET XR** require assessment of renal function prior to initiation of treatment and periodically thereafter. Dosage adjustment might be required based on renal function.

    - **JANUVIA**: For patients with moderate renal impairment (GFR ≥ 30 mL/min to <45 mL/min), the dose is 50 mg once daily. For patients with severe renal impairment (GFR ≥ 15 mL/min to < 30 mL/min) or with end-stage renal disease (ESRD) (GFR < 15 mL/min), including those requiring hemodialysis or peritoneal

dialysis, the dose is 25 mg once daily. JANUVIA may be administered without regard to the timing of dialysis.
    - In patients at 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. **JANUMET** should be discontinued if GFR <45mL/min.
    - JANUMET is not recommended in patients with a GFR ≥ 30 mL/min and < 45 mL/min because these patients require a lower dosage of sitagliptin than what is available in the fixed combination JANUMET product.

Contraindications:

- **JANUVIA** is contraindicated in patients who are hypersensitive to any components of these products and should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

- **JANUMET and JANUMET XR** are contraindicated in patients who are hypersensitive to any components of these products and should not be used in patients with type 1 diabetes, acute or chronic metabolic acidosis (lactic acidosis) or for the treatment of diabetic ketoacidosis (with or without coma), as it would not be effective in these settings.

- **JANUMET** and **JANUMET XR** are contraindicated in patients with severe renal impairment (eGFR below 30 mL/min/1.73 m^2 or GFR < 30mL/min) or acute conditions with potential to alter renal function including dehydration, severe infection or shock. Lower **JANUVIA** dosages are recommended in patients with GFR < 45 mL/min, as well as in ESRD patients requiring hemodialysis or peritoneal dialysis.

- **JANUVIA, JANUMET and JANUMET XR** should be temporarily discontinued in patients undergoing radiologic studies or withholding of food or fluids for surgical or other procedures.

- **JANUMET XR** has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using JANUMET XR.

- Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

Precautions/ Warnings: (Post-marketing Experience/ General)

- Hypersensitivity:
    - **JANUVIA, JANUMET and JANUMET XR** have been reported with serious hypersensitivity reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment especially after the

first dose. If a hypersensitivity reaction is suspected, discontinue **JANUVIA, JANUMET and JANUMET XR** assess for other potential causes, and institute alternative treatment for diabetes.

- Pancreatitis:
  - There have been reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of sitagliptin. If pancreatitis is suspected, **JANUVIA, JANUMET and JANUMET XR** should be discontinued.

- Use in Patients with Renal Impairment:
  - Lower dosages are recommended in patients with GFR < 45 mL/min, as well as in ESRD patients requiring hemodialysis or peritoneal dialysis.

- Hypoglycemia in Combination with a Sulfonylurea or with Insulin:
  - Hypoglycemia has been observed when sitagliptin and metformin (**JANUMET** and **JANUMET XR)** were used in combination with insulin or a sulfonylurea or ethanol. Therefore, to reduce the risk of sulfonylurea- or insulin-induced hypoglycemia, a lower dose of sulfonylurea or insulin may be considered.

- Bullous Pemphigoid:
  - Patients recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor have been reported with cases of bullous pemphigoid requiring hospitalization. Tell patients to report development of blisters or erosions while receiving **JANUVIA, JANUMET and JANUMET XR**. If bullous pemphigoid is suspected, treatments should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

- Lactic Acidosis:
  - Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with **JANUMET** and **JANUMET XR**; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may occur in diabetes mellitus, hepatic impairment, excessive alcohol intake 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. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

<u>Adverse Events:</u>

- The most common adverse experience in sitagliptin monotherapy reported regardless of investigator assessment of causality in >5% of patients was nasopharyngitis. The most

common (>5%) adverse reactions due to initiation of metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache. The most common adverse reactions in the combined extended-release metformin or placebo and *PPAR*γ agonist were hypoglycemia, diarrhea and nausea.

- In the initial therapy of *Combination Therapy with Sitagliptin and Metformin IR,* drug-related adverse reactions reported in ≥1% of patients include diarrhea, nausea, dyspepsia, flatulence, vomiting, headache and hypoglycemia. While in the add-on therapy, the incidences of pre-specified gastrointestinal adverse experiences in patients treated in combination therapy were similar to patients treated with metformin alone including hypoglycemia, diarrhea, nausea, vomiting and abdominal pain.
- *Sitagliptin in Combination with Metformin IR and a Sulfonylurea or Insulin:* the drug-related adverse reactions reported in ≥1% of patients were hypoglycemia, constipation and headache.
- *Sitagliptin in Combination with Metformin IR and a PPAR*γ *Agonist*: the drug-related adverse reactions reported in ≥1% of patients, include headache, diarrhea, nausea, vomiting, hypoglycemia, upper respiratory tract infection, cough, fungal skin infection and peripheral edema.

- **JANUVIA** was generally well tolerated in controlled clinical studies as both monotherapy and combination therapy. In controlled clinical studies, as both monotherapy and combination therapy with metformin or pioglitazone, the overall incidence of adverse reactions, hypoglycemia, and discontinuation of therapy due to clinical adverse reactions with JANUVIA were similar to placebo.

Drug Interactions:

- Carbonic Anhydrase Inhibitors:
  - Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with **JANUVIA, JANUMET and JANUMET XR**, as the risk of lactic acidosis may increase.

- 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. Consider the benefits and risks of concomitant use.

- The Use of Metformin with Other Drugs:
  - Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving **JANUVIA, JANUMET and JANUMET XR** the patient should be closely observed to maintain adequate glycemic control.

Use in Specific Populations:

- Children and adolescents:
  - Safety and effectiveness of **JANUVIA, JANUMET and JANUMET XR** in pediatric patients under 18 years have not been established.

- Pregnancy, breast-feeding and fertility:
  - There are no adequate and well-controlled studies in pregnant women with **JANUVIA, JANUMET and JANUMET XR** or its individual components; therefore, the safety in pregnant women is not known. **JANUVIA, JANUMET and JANUMET XR** should be used during pregnancy only if clearly needed.
  - No studies in lactating animals have been conducted with the combined components of **JANUVIA, JANUMET and JANUMET 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 is excreted in human milk. Therefore, **JANUVIA, JANUMET and JANUMET XR** should not be used by a woman who is nursing.

- Elderly:
  - Because sitagliptin and metformin are substantially excreted by the kidney and because aging can be associated with reduced renal function, **JANUVIA, JANUMET and JANUMET 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.

Before prescribing, please consult the full prescribing information.
Source: prescribing information updated in August & September 2017.

Reference: S-HKPC-MK0431-T-052017a, S-HKPC-MK0431A-T-052017a, HKPC-MK0431A-XRT-122016-1