Product Name: JANUMET 50/500, 50/850 and 50/1 000 mg	Component: English Professional Information Clinical Approval: 17 July 2020 Date Approved: 14 September 2012

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

JANUMET® 50/500 mg Tablets

JANUMET® 50/850 mg Tablets

JANUMET® 50/1 000 mg Tablets

COMPOSITION

JANUMET 50/500 mg: Each tablet contains 50 mg sitagliptin as phosphate and 500 mg metformin hydrochloride.

JANUMET 50/850 mg: Each tablet contains 50 mg sitagliptin as phosphate and 850 mg metformin hydrochloride.

JANUMET 50/1 000 mg: Each tablet contains 50 mg sitagliptin as phosphate and 1 000 mg metformin hydrochloride.

Excipients: microcrystalline cellulose, polyvinylpyrrolidone, sodium lauryl sulphate and sodium stearyl fumarate.

In addition, the film coating contains the following inactive ingredients: black iron oxide, polyvinyl alcohol, polyethylene glycol, red iron oxide, talc and titanium dioxide.

JANUMET is sugar free.

PHARMACOLOGICAL CLASSIFICATION

A.21.2 Oral Hypoglycaemics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Sitagliptin phosphate is a dipeptidyl peptidase 4 (DPP-4) inhibitor and metformin hydrochloride, is a member of the biguanide class.

Sitagliptin phosphate

Sitagliptin phosphate is an inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme with anti-hyperglycaemic activity. The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production.

Metformin hydrochloride

Metformin is an anti-hyperglycaemic medicine which lowers both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilisation.

In patients with type 2 diabetes, administration of single oral doses of sitagliptin leads to inhibition of DPP-4 enzyme activity for a 24-hour period, resulting in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, increased plasma levels of insulin and C-peptide, decreased glucagon concentrations, reduced fasting glucose and reduced glucose excursion following an oral glucose load or a meal.

Cardiac electrophysiology

In a randomised, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of sitagliptin 100 mg, sitagliptin 800 mg (8 times the recommended dose) and placebo. At the recommended dose of 100 mg, there was no effect on the QTc interval obtained at the peak plasma concentration or at any other time during the study. Following the 800 mg dose, the maximum increase in the placebo-corrected mean change in QTc from baseline at 3 hours post-dose was 8,0 msec. This increase was not considered to be clinically significant. At the 800 mg dose, peak sitagliptin plasma concentrations were approximately 11 times higher than the peak concentrations following a 100 mg dose.

In patients with type 2 diabetes administered sitagliptin 100 mg (n=81) or sitagliptin 200 mg (n=63) daily, there were no meaningful changes in QTc interval based on ECG data obtained at the time of expected peak plasma concentration.

Pharmacokinetic properties

Absorption

Sitagliptin phosphate

The absolute bioavailability of sitagliptin is approximately 87 %. Co-administration of a high-fat meal with sitagliptin phosphate had no effect on the pharmacokinetics of sitagliptin.

Metformin hydrochloride

The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50 to 60 %. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1 500 mg and 850 mg to 2 550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alternation in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40 % lower mean peak plasma concentration (C_{max}), a 25 % lower area under the plasma concentration versus time curve (AUC) and a 35 minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Sitagliptin phosphate

The mean volume of distribution at steady-state following a single 100 mg intravenous dose of sitagliptin to healthy subjects is approximately 198 litres. The fraction of sitagliptin reversibly bound to plasma proteins is low (38 %).

Metformin hydrochloride

The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulphonylureas, which are more than 90 % protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride tablets, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally less than 1 µg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 µg/mL, even at maximum doses.

Metabolism

Sitagliptin phosphate

Sitagliptin is primarily eliminated unchanged in urine (79 %) and metabolism is a minor pathway. Following a [^{14}C] sitagliptin oral dose, approximately 16 % of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

Metformin hydrochloride

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Elimination

Sitagliptin phosphate

Following administration of an oral [^{14}C] sitagliptin dose to healthy subjects, approximately 100 % of the administered radioactivity was eliminated in faeces (13 %) or urine (87 %) within one week of dosing. The apparent terminal half-life ($t_{1/2}$) following a 100 mg oral dose of sitagliptin was approximately 12,4 hours and renal clearance was approximately 350 mL/min.

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, ciclosporin, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

Metformin hydrochloride

Renal clearance is approximately 3,5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90 % of the absorbed medicine is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6,2 hours. In blood, the elimination half-life is approximately 17,6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special populations

Renal insufficiency

Sitagliptin phosphate/metformin hydrochloride should not be used in patients with renal insufficiency (see **CONTRAINDICATIONS**).

An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal insufficiency and an approximately 4-fold increase was observed in patients with severe renal insufficiency and in patients with End Stage Renal Disease (ESRD) on haemodialysis, as compared to normal healthy control subjects.

Metformin hydrochloride

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged, and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic insufficiency

Sitagliptin phosphate

In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), mean AUC and C_{max} of sitagliptin increased approximately 21 % and 13 %, respectively, compared to healthy matched controls, following administration of a single 100 mg dose of sitagliptin phosphate. These differences are not considered to be clinically meaningful.

There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score > 9). However, because sitagliptin is primarily renally eliminated, severe hepatic insufficiency is not expected to affect the pharmacokinetics of sitagliptin.

Metformin hydrochloride

No pharmacokinetic studies of metformin have been conducted in patients with hepatic insufficiency.

Elderly

Sitagliptin phosphate

Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin, based on a population pharmacokinetic analysis of Phase I and Phase II data. Elderly subjects (65 to 80 years) had approximately 19 % higher plasma concentrations of sitagliptin compared to younger subjects.

Metformin hydrochloride

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see metformin Professional Information).

INDICATIONS

JANUMET is indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in patients with type 2 diabetes mellitus inadequately controlled with any two of the three agents: metformin, sitagliptin or a sulphonylurea.

JANUMET is also indicated in combination with pioglitazone or with insulin.

JANUMET is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus already being treated with sitagliptin and metformin given separately.

CONTRAINDICATIONS

JANUMET (sitagliptin phosphate/metformin HCl) is contraindicated in patients with:

- known hypersensitivity, including anaphylaxis or angioedema, to sitagliptin phosphate or to other gliptins (DPP-4s inhibitors), metformin hydrochloride or to any other component of JANUMET (see **WARNINGS AND SPECIAL PRECAUTIONS, Sitagliptin phosphate, Hypersensitivity reactions** and **SIDE EFFECTS, Post-Marketing Experience**).

- renal disease or moderate to severe renal dysfunction, e.g. as suggested by serum creatinine levels ≥ 133 µmol/L [males], ≥ 124 µmol/L [females] or creatinine clearance < 50 mL/min.
- acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.
- type 1 diabetes mellitus.
- pregnancy and lactation (see **HUMAN REPRODUCTION**).

JANUMET should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because the use of such products may result in acute alteration of renal function (see **WARNINGS AND SPECIAL PRECAUTIONS, Metformin hydrochloride**).

WARNINGS AND SPECIAL PRECAUTIONS

JANUMET should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis (see **CONTRAINDICATIONS**).

Pancreatitis

In post marketing experience there have been reports of acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotising pancreatitis (see **SIDE EFFECTS, Post-Marketing Experience**), 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, JANUMET and other potentially suspect medicines should be discontinued immediately.

Hypersensitivity reactions

There have been post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of JANUMET. These reactions include anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions usually occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUMET immediately, assess for other potential causes for the event and institute an alternative treatment for diabetes (see CONTRAINDICATIONS and SIDE EFFECTS, Post-Marketing Experience).

Monitoring of renal function

Metformin and sitagliptin are mainly excreted by the kidney. The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive JANUMET (see **CONTRAINDICATIONS**). In patients of advanced age, JANUMET should be carefully titrated to establish the minimum dose for adequate blood glucose lowering effect, as aging can be associated with reduced renal function. In elderly patient's renal function should be monitored regularly.

Before initiation of therapy with JANUMET and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and JANUMET discontinued if evidence of renal impairment is present.

Hypoglycaemia in combination with a sulphonylurea or with insulin

When sitagliptin, a component of JANUMET was used in combination with metformin and a sulphonylurea or insulin, medicines known to cause hypoglycaemia, the incidence of hypoglycaemia was increased over that of placebo in combination with metformin, sulphonylurea or insulin (see **SIDE EFFECTS**). Therefore, to reduce the risk of sulphonylurea- or insulin-induced hypoglycaemia, a lower dose of sulphonylurea or insulin may be considered (see **DOSAGE AND DIRECTIONS FOR USE**).

Metformin hydrochloride

Lactic acidosis

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with JANUMET; when it occurs, it is fatal in approximately 50 % of cases. Lactic acidosis may also occur in association with a number of other pathophysiologic conditions, including when there is significant tissue hypoperfusion and hypoxaemia.

Lactic acidosis is characterised 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.

Reported cases of lactic acidosis have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medicines. 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 reduced 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.

JANUMET should be promptly withheld in the presence of any condition associated with hypoxaemia, dehydration or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, JANUMET 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 JANUMET, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, JANUMET should be temporarily discontinued prior to any intravascular radio-contrast study and for any surgical procedure.

The onset of lactic acidosis often is subtle, and accompanied only by non-specific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence and non-specific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrthymias with more marked acidosis. The patient and the patient's medical practitioner must be aware of the possible importance of such symptoms and the patient should be instructed to notify the medical practitioner immediately if they occur. JANUMET 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 stabilised on any dose level of metformin as in JANUMET, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be medicine 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 < 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explained 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 ketonaemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking JANUMET, the medicine should be discontinued

immediately, and general supportive measures promptly instituted. Because metformin hydrochloride is dialysable (with a clearance of up to 170 mL/min under good haemodynamic conditions), prompt haemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management may result in prompt reversal of symptoms and recovery (see **CONTRAINDICATIONS**).

Hypoglycaemia

Hypoglycaemia does not occur in patients receiving metformin alone under usual circumstances of use but could occur during concomitant use with other glucose-lowering agents (such as sulphonylureas and insulin) or ethanol. Hypoglycaemia may be difficult to recognise in the elderly and in people who are taking β-adrenergic blocking medicine.

Use of concomitant medications that may affect renal function or metformin disposition

Concomitant medicines that may affect renal function or result in significant haemodynamic change or may interfere with the disposition of metformin, such as cationic medicines that are eliminated by renal tubular secretion (see **INTERACTIONS, Metformin hydrochloride**), should be used with caution.

Radiologic studies

Radiologic studies involving the use of intravascular iodinated contrast materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin such as in JANUMET (see **CONTRAINDICATIONS**). Therefore, in

patients in whom any such study is planned, JANUMET should be temporarily discontinued at the time of or prior to the procedure and withheld for 48 hours subsequent to the procedure and re-instituted only after renal function has been re-evaluated and found to be normal.

Hypoxic states

Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterised by hypoxaemia have been associated with lactic acidosis and may also cause prerenal uraemia. When such events occur in patients on JANUMET therapy, the medicine should be promptly discontinued.

Surgical procedures

Use of JANUMET 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.

Alcohol intake

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients should, therefore, be warned against excessive alcohol intake, acute or chronic, while receiving JANUMET.

Impaired hepatic function

Since impaired hepatic function has been associated with lactic acidosis, JANUMET should be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B12 levels

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B12 levels, without clinical manifestations, 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 anaemia. Measurement of haematologic parameters on an annual basis is advised in patients on JANUMET and any apparent abnormalities should be appropriately investigated and managed.

Patients with inadequate Vitamin B12 or calcium intake or absorption appear to be predisposed to developing subnormal Vitamin B12 levels. In these patients, routine serum Vitamin B12 measurements at 2 to 3 year intervals may be useful.

Change in clinical status of patients with previously controlled type 2 diabetes

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

Loss of control of blood glucose

When a patient stabilised on any diabetic regimen is exposed to stress such as fever, trauma, infection or surgery, a temporary loss of glycaemic control may occur. At such times, it may be necessary to withhold JANUMET and temporarily administer insulin. JANUMET may be reinstituted after the acute episode is resolved.

Paediatric use

Safety and effectiveness of JANUMET in paediatric patients below the age of 18 years have not been established.

Use in elderly

JANUMET 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, see (**WARNINGS AND SPECIAL PRECAUTIONS, Monitoring of renal function**).

Laboratory investigations

Sitagliptin phosphate

Across clinical studies, a small increase in white blood cell count (approximately 0,2 x 109/L difference in WBC versus placebo; mean baseline WBC approximately 6,6 x 109/L) was observed due to a small increase in neutrophils.

Severe arthralgia

There have been post-marketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors such as JANUMET. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the drug therapy. Some patients experienced a recurrence of symptoms when restarting JANUMET or a different DPP-4 inhibitor. Consider DPP-4 inhibitors such as JANUMET as a possible cause for severe joint pain and discontinue drug therapy if appropriate.

Effects on ability to drive and use machines

No studies of the effects of JANUMET on the ability to drive and use machines have been performed.

INTERACTIONS

JANUMET

Pharmacokinetic medicine interaction studies with JANUMET have not been performed; however, such studies have been conducted with the individual components of JANUMET, sitagliptin and metformin.

Sitagliptin phosphate

In interaction studies, sitagliptin did not have clinically meaningful effects on the pharmacokinetics of the following: metformin, a thiazolinedione (glitazone), glyburide, simvastatin, warfarin and oral contraceptives. Based on these data, sitagliptin does not

inhibit CYP isozymes CYP3A4, 2C8 or 2C9. Based on *in vitro* data, sitagliptin is also not expected to inhibit CYP2D6, 1A2, 2C19 or 2B6 or to induce CYP3A4.

Population pharmacokinetic analyses have been conducted in patients with type 2 diabetes. Concomitant medicine did not have a clinically meaningful effect on sitagliptin pharmacokinetics. Medicine assessed were those that are commonly administered to patients with type 2 diabetes including cholesterol-lowering agents (e.g. statins, fibrates, ezetimibe), anti-platelet agents (e.g. clopidogrel), antihypertensives (e.g. ACE inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, calcium channel blockers, hydrochlorothiazide), analgesics and non-steroidal anti-inflammatory agents (e.g. naproxen, diclofenac, celecoxib), anti-depressants (e.g. bupropion, fluoxetine, sertraline), antihistamines (e.g. cetirizine), proton-pump inhibitors (e.g. omeprazole, lansoprazole) and medicine for erectile dysfunction (e.g. sildenafil).

There was an increase in the area under the curve (AUC, 11 %) and mean peak medicine concentration (C_{max}, 18 %) of digoxin with the co-administration of sitagliptin.

Patients receiving digoxin should be monitored appropriately. The AUC and C_{max} of sitagliptin were increased approximately 29 % and 68 %, respectively, in subjects with co-administration of a single 100 mg oral dose of JANUVIA and a single 600 mg oral dose of ciclosporin, a potent probe inhibitor of p-glycoprotein. The observed changes in sitagliptin pharmacokinetics are not considered to be clinically meaningful.

Metformin hydrochloride

Glyburide: In a single-dose interaction study in type 2 diabetes patients, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

Furosemide: A single-dose, metformin-furosemide interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max} by 22 % and blood AUC by 15 %, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31 % and 12 % smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32 %, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine: A single-dose, metformin-nifedipine interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20 % and 9 %, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic medicines: Cationic medicines (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. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose metformin-cimetidine interaction studies, with a 60 % increase in peak metformin plasma and whole blood concentrations and a 40 % increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of JANUMET and/or the interfering medicine is recommended in patients who are taking cationic medicines that are excreted via the proximal renal tubular secretory system.

Other: Certain medicines tend to produce hyperglycaemia and may lead to loss of glycaemic control. These medicines include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid hormones, oestrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking medicines and isoniazid. When such medicines are administered to a patient receiving JANUMET the patient should be closely observed to maintain adequate glycaemic control.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound medicines such as salicylates, sulphonamides, chloramphenicol and probenecid, as compared to the sulphonylureas, which are extensively bound to serum proteins.

HUMAN REPRODUCTION

JANUMET is contraindicated in pregnancy and lactation

Lactation

JANUMET should not be used by a woman who is breastfeeding an infant.

DOSAGE AND DIRECTIONS FOR USE

General

The dosage of anti-hyperglycaemic therapy with JANUMET should be individualised on the basis of the patient's current regimen, effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin.

JANUMET should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastro-intestinal (GI) side effects associated with metformin.

Dosing recommendations

The starting dose of JANUMET should be based on the patient's current regimen.

JANUMET should be given twice daily with meals. The following doses are available:

50 mg sitagliptin/500 mg metformin hydrochloride

50 mg sitagliptin/850 mg metformin hydrochloride

50 mg sitagliptin/1 000 mg metformin hydrochloride.

For patients switching from co-administration of sitagliptin and metformin

For patients switching from co-administration of sitagliptin and metformin, JANUMET may be initiated at the dose of sitagliptin and metformin already being taken.

For patients inadequately controlled on dual combination therapy with any two of the following three anti-hyperglycaemic agents: sitagliptin, metformin or a sulphonylurea

The usual starting dose of JANUMET should provide 100 mg total daily dose of sitagliptin. In determining the starting dose of the metformin component, the patient's level of glycaemic control and current dose (if any) of metformin should be considered. Gradual dose escalation to reduce the gastro-intestinal (GI) side effects associated with metformin should be considered. Patients currently on or initiating a sulphonylurea may require lower sulphonylurea doses to reduce the risk of sulphonylurea-induced hypoglycaemia (see **SIDE EFFECTS**).

For patients inadequately controlled on dual combination therapy with any two of the following three anti-hyperglycaemic agents: sitagliptin, metformin or insulin

The usual starting dose of JANUMET should provide 100 mg total daily dose of sitagliptin. In determining the starting dose of the metformin component, the patient's level of glycaemic control and current dose (if any) of metformin should be considered. Gradual dose

escalation to reduce the gastrointestinal (GI) side effects associated with metformin should be considered. Patients currently on or initiating insulin therapy may require lower doses of insulin to reduce the risk of hypoglycaemia (see **WARNINGS AND SPECIAL PRECAUTIONS**).

No studies have been performed specifically examining the safety and efficacy of JANUMET in patients previously treated with other oral anti-hyperglycaemic agents and switched to JANUMET. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycaemic control can occur.

Patients with renal insufficiency

JANUMET should not be used in patients with renal failure or renal dysfunction e.g. serum creatinine levels ≥ 133 µmol/L [males], ≥ 124 µmol/L [females] or abnormal creatinine clearance (see **CONTRAINDICATIONS**).

Elderly

As metformin and sitagliptin are excreted by the kidney, JANUMET should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly (see **SIDE EFFECTS, Metformin hydrochloride, Lactic acidosis**).

Paediatric population

JANUMET is not recommended for use in children below 18 years of age due to lack of data on its safety and efficacy in this population.

SIDE EFFECTS

Adverse reactions considered as medicine related reported in excess (> 0,2 % and difference > 1 patient) of placebo and in patients receiving JANUMET in double-blind studies are listed below as MedDRA preferred term by system organ class and absolute frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000).

Sitagliptin with Metformin

Nervous system disorders

Common: somnolence

Gastrointestinal disorders

Common: nausea

Uncommon: diarrhoea

Uncommon: upper abdominal pain

Investigations

Uncommon: blood glucose decreased.

Sitagliptin with Metformin and a Sulphonylurea

Metabolism and nutrition disorders

Common: hypoglycaemia

Respiratory, thoracic and mediastinal

Uncommon: rhinorrhoea

Gastrointestinal disorders

Common: constipation

Uncommon: nausea.

Sitagliptin with Metformin and a PPARγ Agonist

Metabolism and nutrition disorders

Common: hypoglycaemia

General disorders and administration site conditions

Common: peripheral oedema.

Sitagliptin with Metformin and Insulin

Metabolism and nutrition disorders

Very common: hypoglycaemia

Nervous system disorders

Uncommon: headache

Gastrointestinal disorders

Uncommon: dry mouth.

Additional information on the individual active substances of the fixed dose combination:

Sitagliptin

In addition, in monotherapy studies of up to 24 weeks in duration of sitagliptin 100 mg once daily alone compared to placebo, adverse reactions considered as medicine-related reported

in patients treated with sitagliptin in excess (> 0,2 % and difference more than 1 patient) of that in patients receiving placebo are headache, hypoglycaemia, constipation and dizziness.

In addition to the medicine-related adverse reactions described above, adverse events reported regardless of causal relationship to medication and occurring in at least 5 %, and more commonly in patients treated with sitagliptin included upper respiratory tract infection and nasopharyngitis. Additional adverse events that occurred more frequently in patients treated with sitagliptin (not reaching the 5 % level but occurring with an incidence of > 0,5 % higher with sitagliptin than that in the control group) included osteoarthritis and pain in extremity.

Post-Marketing Experience

During post-marketing experience of JANUMET or sitagliptin, one of the active substances of JANUMET, the following additional adverse reactions were reported (frequency not known): hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis and exfoliative skin conditions including Stevens-Johnson syndrome (see **WARNINGS AND SPECIAL PRECAUTIONS**): acute pancreatitis, including fatal and non-fatal haemorrhagic and necrotising pancreatitis (see **WARNINGS AND SPECIAL PRECAUTIONS, Pancreatitis**); worsening renal function, including acute renal failure (sometimes requiring dialysis); upper respiratory tract infection; nasopharyngitis; constipation, vomiting; headache, severe and disabling arthralgia (see **WARNINGS AND SPECIAL PRECAUTIONS**); myalgia; pain in extremity; back pain.

Metformin

Established adverse reactions with metformin

The following side effects may occur with metformin:

Metabolism and nutrition disorders

Very rare: decrease of vitamin B12 and folic acid absorption with decrease of serum levels during long-term use of metformin

Very rare: lactic acidosis (see **WARNINGS AND SPECIAL PRECAUTIONS**)

Nervous system disorders

Common: metallic taste

Gastrointestinal disorders

Very common: gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These side effects occur most frequently during initiation of therapy and resolve spontaneously in most cases.

Skin and subcutaneous tissue disorders

Very rare: mild erythema in some hypersensitive individuals.

KNOWN SYMPTOMS OF OVER DOSAGE AND PARTICULARS OF ITS TREATMENT

Sitagliptin phosphate

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g. remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram) and institute supportive therapy if required.

Sitagliptin is modestly dialysable. In clinical studies, approximately 13,5 % of the dose was removed over a 3- to 4-hour haemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.

Metformin hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts > 50 grams. Hypoglycaemia was reported in approximately 10 % of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32 % of metformin overdose cases (see **SIDE EFFECTS, Metformin hydrochloride**). Metformin is dialysable with a clearance of up to 170 mL/min under good haemodynamic conditions. Therefore, haemodialysis may be useful for removal of accumulated medicine from patients in whom metformin overdosage is suspected.

IDENTIFICATION

JANUMET 50/500 mg: A light pink, capsule-shaped film-coated tablet, debossed 575 on one side and blank on the other.

JANUMET 50/850 mg: A pink, capsule-shaped film-coated tablet, debossed 515 on one side and blank on the other.

JANUMET 50/1 000 mg: A red, capsule-shaped film-coated tablet, debossed 577 on one side and blank on the other.

PRESENTATION

JANUMET Tablets will be packaged in opaque PVC/PE/PVDC aluminium push through blisters in packs of 56 tablets with blisters containing 14 tablets.

STORAGE INSTRUCTIONS

Store at or below 30 °C.

Keep out of reach of children.

REGISTRATION NUMBERS

JANUMET 50/500 mg: 42/21.2/1089

JANUMET 50/850 mg: 42/21.2/1090

JANUMET 50/1 000 mg: 42/21.2/1091

NAME AND ADDRESS OF THE HOLDER OF THE CERTIFICATION OF REGISTRATION

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DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION

Date of registration: 14 September 2012

Date of the most recent revision: 17 July 2020

WPC-MK0431-T-042012