SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

JANUMET® 50 mg/500 mg Tablets

JANUMET® 50 mg/850 mg Tablets

JANUMET® 50 mg/1 000 mg Tablets

COMPOSITION

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

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

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

JANUMET is sugar free.

Inactive ingredients: Microcrystalline cellulose, polyvinylpyrrolidone, sodium lauryl sulphate and sodium stearyl fumarate.

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

PHARMACOLOGICAL CLASSIFICATION

A.21.2 Oral Hypoglycaemics

PHARMACOLOGICAL ACTION

Mechanism of Action

Sitagliptin phosphate/metformin hydrochloride is a combination of two antihyperglycaemic agents with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: Sitagliptin phosphate, a dipeptidyl peptidase 4 (DPP-4) inhibitor and metformin hydrochloride, a member of the biguanide class.

Sitagliptin phosphate

Sitagliptin phosphate is an orally-active, potent and selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. 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 antihyperglycaemic agent which lowers both basal and postprandial plasma glucose. Its pharmacologic mechanism of action are different from other classes of oral antihyperglycaemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilisation.

Pharmacodynamics

Sitagliptin phosphate

General

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.

In Phase III clinical studies of 18 and 24 week duration, treatment with sitagliptin 100 mg daily in patients with type 2 diabetes significantly improved beta cell function, as assessed by several markers, including HOMA-β (Homeostasis Model Assessment-β), proinsulin to insulin ratio and measures of beta cell responsiveness from the frequently-sampled meal tolerance test. In Phase II studies, sitagliptin 50 mg twice daily provided similar glycaemic efficacy compared to sitagliptin 100 mg once daily.

In a randomised, placebo-controlled, double-blind, double-dummy, four-period crossover 2 day study in healthy adult subjects, the effects on post-meal plasma concentrations of active and total GLP-1 and glucose after co-administration of sitagliptin and metformin were compared with those after administration of sitagliptin alone, metformin alone or placebo each administered for 2 days. The incremental 4-hour post-meal weighted mean active GLP-1 concentrations were increased approximately 2-fold, after either administration of sitagliptin alone or metformin alone compared with placebo. The effect on active GLP-1 concentrations after co-administration of sitagliptin and metformin were additive, with active GLP-1 concentrations increased by approximately 4-fold compared with placebo. Sitagliptin alone increased only active GLP-1 concentrations, reflecting inhibition of DPP-4, whereas metformin alone increased active and total GLP-1 concentrations to a similar extent. These data are consistent with different mechanisms for the increase in active GLP-1 concentrations. Results from the study also demonstrated that sitagliptin but not metformin, enhances active GIP concentrations.

In studies with healthy subjects, sitagliptin did not lower blood glucose levels or cause hypoglycaemia, suggesting that the insulinotropic and glucagon suppressive actions of the medicine are glucose dependent.

Effects on blood pressure

In a randomised, placebo-controlled crossover study in hypertensive patients on one or more anti-hypertensive medicines (including angiotensin-converting enzyme inhibitors, angiotensin-II antagonists, calcium-channel blockers, beta-blockers and diuretics), co-administration with sitagliptin was generally well tolerated. In these patients, sitagliptin had a modest blood pressure lowering effect; 100 mg per day of sitagliptin reduced 24-hour mean ambulatory systolic blood pressure by approximately 2 mm Hg, as compared to placebo. Reductions have not been observed in subjects with normal blood pressure.

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 small 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.

Pharmacokinetics

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 vs. 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 litre. 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 mcg/ml. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/ml, even at maximum doses.

Metabolism

Sitagliptin phosphate

Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79 % of sitagliptin is excreted unchanged in the urine. 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 $t_{1/2}$ 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

Type 2 diabetes

Sitagliptin phosphate

The pharmacokinetics of sitagliptin in patients with type 2 diabetes are generally similar to those in healthy subjects.

Metformin hydrochloride

In the presence of normal renal function, there are no differences between single- or multiple-dose pharmacokinetics of metformin between patients with type 2 diabetes and normal subjects, nor is there any accumulation of metformin in either group at usual clinical doses.

Renal insufficiency

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

Sitagliptin phosphate

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 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.

Gender

Sitagliptin phosphate

Gender had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data, and on a population pharmacokinetic analysis of Phase I and Phase II data.

Metformin hydrochloride

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analysed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycaemic effect of metformin was comparable in males and females.

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 package insert).

Treatment with sitagliptin and metformin combination tablets should not be initiated in patients 80 years of age or older, unless measurement of creatinine clearance demonstrates that renal function is not reduced (see **"SIDE EFFECTS AND SPECIAL PRECAUTIONS, Special Precautions**, **Metformin hydrochloride"**).

Paediatric

No studies have been performed in paediatric patients.

Body Mass Index (BMI)

Sitagliptin phosphate

Body mass index (BMI) had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data, and on a population pharmacokinetic analysis of Phase I and Phase II data.

INDICATIONS

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.

JANUMET is also 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.

CONTRAINDICATIONS

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

1. Known hypersensitivity to sitagliptin phosphate, metformin hydrochloride or any other component of JANUMET (see **"SIDE EFFECTS AND SPECIAL PRECAUTIONS, Special Precautions, Sitagliptin phosphate, Hypersensitivity reactions"** and **"Side Effects, Post-marketing data"**).
2. Renal disease or renal dysfunction e.g. as suggested by serum creatinine levels ≥ 133 micromol/l [males], ≥ 124 micromol/l [females], or abnormal creatinine clearance which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction and septicaemia.

3. Acute or chronic metabolic acidosis including diabetic ketoacidosis, with or without coma.

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 **"SIDE EFFECTS AND SPECIAL PRECAUTIONS, Special Precautions, Metformin hydrochloride"**).

A history of severe hypersensitivity reaction, such as anaphylaxis or angioedema to JANUMET or any other gliptins (DPP-4).

WARNINGS

See also **"SIDE EFFECTS AND SPECIAL PRECAUTIONS, Special Precautions"**.

Pancreatitis

In post-marketing experience there have been reports of acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotising pancreatitis (see **"SIDE EFFECTS AND SPECIAL PRECAUTIONS, Side Effects**, **Post-marketing data"**), 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 medicinal products 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 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, and institute an alternative class of

medicines for treatment for diabetes (see "CONTRAINDICATIONS" and "SIDE EFFECTS AND SPECIAL PRECAUTIONS, Side Effects, Post-marketing data").

Use in the elderly

As metformin and sitagliptin are excreted by the kidneys, 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 AND SPECIAL PRECAUTIONS, Special Precautions, Metformin hydrochloride, Lactic acidosis"**).

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 medicine interaction studies, sitagliptin did not have clinically meaningful effects on the pharmacokinetics of the following: Metformin, rosiglitazone, glyburide, simvastatin, warfarin and oral contraceptives. Based on these data, sitagliptin does not inhibit CYP isoenzymes 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 medications did not have a clinically meaningful effect on sitagliptin pharmacokinetics. Medications 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, 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, lansoprozole), and medications for erectile dysfunction (e.g. sildenafil).

There was a slight 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. These increases are not considered to be clinically meaningful. 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 medicine 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 medicine 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 medicine 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 medications, 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 products, estrogens, 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.

PREGNANCY AND LACTATION

Pregnancy

There are no adequate and well-controlled studies in pregnant women with JANUMET or its individual components; therefore, the safety of JANUMET in pregnant women is not known. JANUMET is not recommended for use in pregnancy.

Lactation

No studies in lactating animals have been conducted with the combined components of JANUMET. JANUMET should not be used by a woman who is breastfeeding an infant.

DOSAGE AND DIRECTIONS FOR USE

General

The dosage of antihyperglycaemic 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 gastrointestinal (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 antihyperglycaemic agents: Sitagliptin, metformin or a sulphonylurea

The usual starting dose of JANUMET should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose). In determining the starting dose of the metformin component, the patient's level of glycaemic control and current dose 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 a sulphonylurea may require lower sulphonylurea doses to reduce the risk of sulphonylurea-induced hypoglycaemia (see **"SIDE EFFECTS AND SPECIAL PRECAUTIONS"**).

No studies have been performed specifically examining the safety and efficacy of JANUMET, in patients previously treated with other oral antihyperglycaemic 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 micromol/l [males], ≥ 124 micromol/l [females] or abnormal creatinine clearance (see **"CONTRAINDICATIONS"**).

Elderly

As metformin and sitagliptin are excreted by the kidneys, 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 AND SPECIAL PRECAUTIONS, Special Precautions, 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 AND SPECIAL PRECAUTIONS

Side Effects

JANUMET

Adverse reactions considered as medicine-related reported in excess (> 0,2 % and difference > 1 patient) of placebo and in patients receiving sitagliptin in combination with metformin (the components of JANUMET) in double-blind studies, are listed below as MedDRA preferred term by system organ class and absolute frequency (**Table 1**). Frequencies are defined as: Very common (≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1 000, < 1/100); Rare (≥ 1/10 000, < 1/1 000); Very rare (< 1/10 000).

Table 1

The frequency of adverse reactions identified from placebo-controlled clinical studies

Adverse Reaction	**Frequency of adverse reaction by treatment regimen**	
	Sitagliptin with Metformin	**Sitagliptin with Metformin and a Sulphonylurea**
Investigations		
Decreased blood glucose levels	Uncommon	
Nervous system disorders		
Somnolence	Uncommon	

Gastrointestinal disorders		
Diarrhoea	Uncommon	
Nausea	Common	
Constipation		Common
Upper abdominal pain	Uncommon	
Metabolism and nutrition disorders		
Hypoglycaemia		Very common

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 > 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 medicinal product) 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 greater than 0,5 % higher with sitagliptin than that in the control group), included osteoarthritis and pain in extremity.

Post-marketing data

During post-marketing experience of JANUMET or sitagliptin, one of the active substances of JANUMET, the following additional adverse reactions have been reported (frequency not known): Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome (see **"SIDE EFFECTS AND SPECIAL PRECAUTIONS, Special Precautions"**); acute pancreatitis, including fatal and non-

fatal haemorrhagic and necrotising pancreatitis (see **"WARNINGS, Pancreatitis"**); worsening renal function, including acute renal failure (sometimes requiring dialysis); upper respiratory tract infection; nasopharyngitis; constipation, vomiting; headache.

Metformin

Established adverse reactions with metformin

The following side effects may occur with Metformin.

Frequencies are defined as follows:

Very common: > 1/10; Common: ≥ 1/100, < 1/10; Uncommon: ≥ 1/1 000; < 1/100; Rare: ≥ 1/10 000, < 1/1 000; Very rare: ≤ 1/10 000, including isolated reports.

Metabolism and nutrition disorders

Very rare: Decrease of vitamin B_{12} and folic acid absorption with decrease of serum levels during long-term use of metformin. This change is generally without clinical significance.

Very rare: Lactic acidosis (see **"SIDE EFFECTS AND SPECIAL PRECAUTIONS, 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.

Special Precautions

JANUMET

JANUMET should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Monitoring of renal function: Metformin and sitagliptin are known to be substantially excreted by the kidneys. 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. In patients with advanced age, JANUMET should be carefully titrated to establish the minimum dose for adequate glycaemic effect, because aging can be associated with reduced renal function. In elderly patients, particularly those 80 years of age or older, 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: When sitagliptin, a component of JANUMET was used in combination with metformin and a sulphonylurea, a medication known to cause hypoglycaemia, the incidence of sulphonylurea-induced hypoglycaemia was increased over that of placebo in combination with metformin and a sulphonylurea (see **"SIDE EFFECTS AND SPECIAL PRECAUTIONS"**). Therefore, to reduce the risk of sulphonylurea-induced hypoglycaemia, a lower dose of sulphonylurea may be considered (see **"DOSAGE AND DIRECTIONS FOR USE"**). The use of JANUMET in combination with insulin has not been studied.

Sitagliptin phosphate

Hypoglycaemia in combination with a sulphonylurea: In clinical trials of sitagliptin as monotherapy and as part of combination therapy with agents not known to cause hypoglycaemia (i.e. metformin or pioglitazone), rates of hypoglycaemia reported with sitagliptin were similar to rates in patients taking placebo. As typical with other antihyperglycaemic agents used in

combination with a sulphonylurea, when sitagliptin was used in combination with a sulphonylurea, a medication known to cause hypoglycaemia, the incidence of sulphonylurea-induced hypoglycaemia was increased over that of placebo (see **"SIDE EFFECTS AND SPECIAL PRECAUTIONS"**). Therefore, to reduce the risk of sulphonylurea-induced hypoglycaemia, a lower dose of sulphonylurea may be considered (see **"DOSAGE AND DIRECTIONS FOR USE"**). The use of sitagliptin in combination with insulin has not been adequately studied.

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. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to medicine exposure. Onset of these reactions 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, assess for other potential causes for the event, and institute alternative treatment for diabetes (see **"CONTRAINDICATIONS"** and **"SIDE EFFECTS AND SPECIAL PRECAUTIONS, Side Effects**, **Post-marketing data"**).

Metformin hydrochloride

Lactic acidosis: Lactic acidosis is a rare, but serious metabolic complication that can occur due to metformin accumulation during treatment with JANUMET (sitagliptin phosphate/metformin hydrochloride); 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 hypoxaemia. Lactic acidosis is characterised by elevated blood lactate levels (> 5 mmol/litre), 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 greater than 5 mcg/ml are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0,03 cases/1 000 patient-years, with approximately 0,015 fatal cases/1 000 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 insufficiency, 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 hypoxaemia, 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. Metformin treatment should not be initiated in patients 80 years of age or older, unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, metformin 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, 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 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 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. 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 stabilised on any dose level of metformin, 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 less than 5 mmol/litre 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.

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 metformin, 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 often results 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 when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulphonylureas and insulin) or ethanol. Elderly, debilitated or

malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycaemic effects. Hypoglycaemia may be difficult to recognise in the elderly, and in people who are taking β-adrenergic blocking medicines.

Use of concomitant medications that may affect renal function or metformin disposition: Concomitant medication(s) 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 involving the use of intravascular iodinated contrast materials (e.g. intravenous urogram, intravenous cholangiography, angiography and computed tomography (CT) scans with intravascular contrast materials): Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function, and have been associated with lactic acidosis in patients receiving metformin (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 reinstituted 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 pre-renal azotaemia. 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 some cases of lactic acidosis, JANUMET should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

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 anaemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation. Measurement of haematologic parameters on an annual basis is advised in patients on JANUMET and any apparent abnormalities should be appropriately investigated and managed.

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 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 under 18 years have not been established.

Use in the elderly

JANUMET

Because sitagliptin and metformin are substantially excreted by the kidney and because aging can be associated with reduced renal function, 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 **"SIDE EFFECTS AND SPECIAL PRECAUTIONS, Special Precautions, Monitoring of renal function"**).

Sitagliptin phosphate

In clinical studies, the safety and effectiveness of sitagliptin in the elderly (65 years or older) were comparable to those seen in younger patients (65 years or younger).

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Metformin is known to be substantially excreted by the kidneys and because the risk of serious adverse reactions to the medicine is greater in patients with impaired renal function, metformin should only be used in patients with normal renal function (see **"CONTRAINDICATIONS"**).

Laboratory test findings

Sitagliptin phosphate

The incidence of laboratory adverse experiences was similar in patients treated with sitagliptin and metformin compared to patients treated with placebo and metformin. Across clinical studies, a small increase in white blood cell count (approximately 200 cells/microlitre in WBC vs. placebo; mean baseline WBC approximately 6 600 cells/microlitre) was observed due to a small increase in neutrophils. This observation was seen in most but not all studies. This change in laboratory parameters is not considered to be clinically relevant.

Metformin hydrochloride

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 anaemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation (see **"SIDE-EFFECTS AND SPECIAL PRECAUTIONS, Special Precautions, Metformin hydrochloride"**).

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. However, JANUMET is not expected to affect the ability to drive and use machines.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Sitagliptin phosphate

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were generally well tolerated. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin (see **"PHARMACOLOGICAL ACTION, Pharmacodynamics, Cardiac electrophysiology"**). There is no experience with doses above 800 mg in humans. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for 10 days and 400 mg per day for periods of up to 28 days.

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 greater than 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 AND SPECIAL PRECAUTIONS, Special Precautions, 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 are packed in opaque PVC/PE/PVDC, aluminium push through blisters in packs of 28 or 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

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