

DATA SHEET

1. PRODUCT NAME

JANUMET® 50/500 mg film-coated tablets

JANUMET® 50/850 mg film-coated tablets

JANUMET® 50/1000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each JANUMET 50/500 mg tablet contains sitagliptin phosphate monohydrate equivalent to 50 mg of sitagliptin and 500 mg of metformin hydrochloride.

Each JANUMET 50/850 mg tablet contains sitagliptin phosphate monohydrate equivalent to 50 mg of sitagliptin and 850 mg of metformin hydrochloride.

Each JANUMET 50/1000 mg tablet contains sitagliptin phosphate monohydrate equivalent to 50 mg of sitagliptin and 1000 mg of metformin hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

50/500 mg tablets: Light pink, film coated tablet, debossed "575" on one side and plain on the other.

50/850 mg tablets: Pink, film coated tablet, debossed "515" on one side and plain on the other.

50/1000 mg tablets: Red, film coated tablet, debossed "577" on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

JANUMET is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus inadequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.

JANUMET is indicated as part of triple combination therapy with a sulfonylurea 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 sulfonylurea.

JANUMET is indicated in patients with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control in combination with premixed or long/intermediate acting insulin.

4.2 Dose and method of administration

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 gastrointestinal (GI) adverse effects associated with metformin.

Dosage 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/1000 mg metformin hydrochloride

For patients inadequately controlled on metformin monotherapy

For patients inadequately controlled on metformin alone, the usual starting dose of JANUMET should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose), plus the dose of metformin already being taken.

For patients inadequately controlled on sitagliptin monotherapy

For patients inadequately controlled on sitagliptin alone, the usual starting dose of JANUMET is 50 mg sitagliptin/500 mg metformin hydrochloride twice daily. Patients may be titrated up to 50 mg sitagliptin/1000 mg metformin hydrochloride twice daily. Patients taking sitagliptin monotherapy dose-adjusted for renal impairment should not be switched to JANUMET (see 4.3 Contraindications).

For patients switching from coadministration of sitagliptin and metformin

For patients switching from coadministration 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 sulfonylurea

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 (if any) of metformin should be considered. Gradual dose escalation to reduce the gastrointestinal (GI) adverse effects associated with metformin should be considered. Patients currently on or initiating a sulfonylurea may require lower sulfonylurea doses to reduce the risk of sulfonylurea-induced hypoglycaemia (See 4.4 Special warnings and precautions for use).

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

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 (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 4.4 Special warnings and precautions for use).

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.

Recommendations for use in renal impairment

Assess renal function prior to initiation of JANUMET and periodically thereafter.

JANUMET is contraindicated in patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m² (see 4.3 Contraindications and 4.4 Special warnings and precautions for use).

JANUMET is not recommended in patients with an eGFR ≥ 30 mL/min/1.73 m² and < 45 mL/min/1.73 m² because these patients require a lower dosage of sitagliptin than what is available in the fixed combination JANUMET product.

Discontinuation for iodinated contrast imaging procedures:

Discontinue JANUMET at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR ≥ 30 to < 60 mL/min/1.73 m²; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart JANUMET if renal function is acceptable (see 4.4 Special warnings and precautions for use).

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 4.4 Special warnings and precautions for use, 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.

4.3 Contraindications

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

1. Severe renal impairment (eGFR < 30 mL/min/1.73 m²) (see 4.4 Special warnings and precautions for use, *Metformin hydrochloride, Renal impairment*).
2. Known hypersensitivity to sitagliptin phosphate, metformin hydrochloride or any other component of JANUMET (See 4.4 Special warnings and precautions for use, Sitagliptin phosphate, Hypersensitivity reactions and 4.8 Undesirable effects, Postmarketing experience).
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 4.4 Special warnings and precautions for use; Metformin hydrochloride)

4.4 Special warnings and precautions for use

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

Pancreatitis: There have been reports of acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotising pancreatitis (see 4.8 Undesirable effects), 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.

Monitoring of renal function

Metformin and sitagliptin are known to be substantially excreted by the kidney. The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. JANUMET is contraindicated in severe renal impairment, patients with an eGFR

< 30 mL/min/1.73 m² (see 4.2 Dose and method of administration, 4.3 Contraindications and 4.4 Special warnings and precautions for use, *Metformin hydrochloride, Lactic acidosis*).

Before initiation of therapy with JANUMET and at least annually thereafter, renal function should be assessed. 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 sulfonylurea or with insulin: As is typical with other anti-hyperglycaemic agents, when sitagliptin was used in combination with metformin, and a sulfonylurea or insulin, medications known to cause hypoglycaemia, the incidence of sulfonylurea- or insulin-induced hypoglycaemia was increased over that of placebo in combination with metformin, a sulfonylurea or insulin (see 4.8 Undesirable effects). Therefore, to reduce the risk of sulfonylurea- or insulin-induced hypoglycaemia, a lower dose of sulfonylurea or insulin may be considered (see 4.2 Dose and method of administration).

Sitagliptin phosphate

Hypoglycaemia in combination with a sulfonylurea or with insulin: In clinical trials of sitagliptin as monotherapy and as part of combination therapy with agents not known to cause hypoglycaemia (i.e. metformin or a PPAR γ agonist (thiazolidinedione)), rates of hypoglycaemia reported with sitagliptin were similar to rates in patients taking placebo. As is typical with other anti-hyperglycaemic agents, when sitagliptin was used in combination with a sulfonylurea or insulin, medications known to cause hypoglycaemia, the incidence of sulfonylurea- or insulin-induced hypoglycaemia was increased over that of placebo (see 4.8 Undesirable effects). Therefore, to reduce the risk of sulfonylurea- or insulin-induced hypoglycaemia, a lower dose of sulfonylurea or insulin may be considered (see 4.2 Dose and method of administration).

Hypersensitivity reactions: There have been postmarketing 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 4.3 Contraindications and 4.8 Undesirable effects, *Postmarketing experience*).

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

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 HCl); 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/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 μ g/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications (see 4.2 Dose and method of administration, *Recommendations for use in renal impairment*). 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 (see Use in the elderly, *Metformin hydrochloride*).

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 radiocontrast 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/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

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 4.3 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 sulfonylureas 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 (for example, 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 4.3 Contraindications). Therefore, in patients with an eGFR ≥ 30 to < 60 mL/min/1.73 m², in patients with a history of hepatic impairment, alcoholism, or heart failure, or in patients who will be administered intra-arterial iodinated contrast, JANUMET should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstated only after renal function has been re-evaluated and found to be acceptable (see 4.2 Dose and method of administration).

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 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 acceptable (see 4.2 Dose and method of administration).

Alcohol intake: Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should 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 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, is, however, very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B₁₂ 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 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 two- to three-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 reinstated 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 4.4 Special warnings and precautions for use, Monitoring of renal function).

Sitagliptin phosphate

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

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.

4.5 Interaction with other medicines and other forms of interaction

Sitagliptin and metformin

Coadministration of multiple doses of sitagliptin (50 mg b.i.d) and metformin (1000 mg b.i.d) did not meaningfully alter the pharmacokinetics of either sitagliptin or metformin in patients with type 2 diabetes.

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 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 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), 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 coadministration 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 coadministration of a single 100-mg oral dose of JANUVIA[®] and a single 600-mg oral dose of cyclosporine, 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, coadministration 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 coadministration. 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 coadministered chronically.

Nifedipine: A single-dose, metformin-nifedipine medicine interaction study in normal healthy volunteers demonstrated that coadministration 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.

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.

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 coadministered 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, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

4.6 Fertility, pregnancy and lactation

Pregnancy

JANUMET

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, like other oral anti-hyperglycaemic agents, is not recommended for use in pregnancy.

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

Sitagliptin phosphate

Sitagliptin was not teratogenic in rats at oral doses up to 250 mg/kg or in rabbits given up to 125 mg/kg during organogenesis (up to 32 and 22 times, respectively, the human exposure based on the recommended daily adult human dose of 100 mg/day). In rats, a slight increase in the incidence of foetal rib malformations (absent, hypoplastic and wavy ribs) was observed at oral doses of 1000 mg/kg/day (approximately 100 times the human exposure based on the recommended daily adult human dose of 100 mg/day). Slight decreases in mean preweaning body weights of both sexes and postweaning body weight gains of males were observed in the offspring of rats given oral dose of 1000 mg/kg/day. However, animal reproduction studies are not always predictive of the human response.

Metformin hydrochloride

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

Nursing mothers

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

4.7 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.

4.8 Undesirable effects

In placebo-controlled clinical trials, in patients with type 2 diabetes mellitus, the combination of sitagliptin and metformin was generally well tolerated. The overall incidence of adverse effects reported in patients receiving the combination of sitagliptin and metformin was similar to that reported in patients receiving the combination of placebo and metformin.

Combination therapy with sitagliptin and metformin

Initial therapy

In a 24-week placebo-controlled factorial study of initial therapy with sitagliptin 50 mg twice daily in combination with metformin at 500 or 1000 mg twice daily, the medicine-related adverse reactions reported in $\geq 1\%$ of patients receiving combination therapy (and greater than in patients receiving placebo) are shown in Table 1.

Table 1 Initial Therapy with Combination of Sitagliptin and Metformin: Medicine-Related Adverse Reactions Reported in \geq 1% of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Placebo)[†]				
	Number of Patients (%)			
	Placebo	Sitagliptin 100 mg q.d.	Metformin 500 or 1000 mg b.i.d. ^{††}	Sitagliptin 50 mg b.i.d. + Metformin 500 or 1000 mg b.i.d. ^{††}
	N = 176	N = 179	N = 364	N = 372
Diarrhoea	2 (1.1)	0 (0.0)	12 (3.3)	13 (3.5)
Nausea	1 (0.6)	0 (0.0)	9 (2.5)	6 (1.6)
Dyspepsia	0 (0.0)	0 (0.0)	4 (1.1)	5 (1.3)
Flatulence	0 (0.0)	0 (0.0)	2 (0.5)	5 (1.3)
Vomiting	0 (0.0)	0 (0.0)	1 (0.3)	4 (1.1)
Headache	0 (0.0)	1 (0.6)	4 (1.1)	5 (1.3)
Hypoglycaemia	0 (0.0)	1 (0.6)	2 (0.5)	4 (1.1)
[†] Intent-to-treat population				
^{††} Data pooled for the patients given the lower and higher doses of metformin.				

Add-on combination therapy to metformin

In a 24-week placebo-controlled study of sitagliptin added to ongoing metformin therapy, 464 patients on metformin were treated with sitagliptin 100 mg once daily and 237 patients were given placebo with metformin. The only medicine-related adverse reaction reported that occurred with an incidence of \geq 1% and higher than placebo in patients receiving sitagliptin and metformin was nausea (100 mg sitagliptin and metformin, 1.1%; placebo and metformin, 0.4%).

Hypoglycaemia and gastrointestinal adverse experiences

In the placebo-controlled studies of combination therapy with sitagliptin and metformin, the incidence of hypoglycaemia (regardless of investigator assessment of causality) reported in patients treated with the combination of sitagliptin and metformin was similar to that reported for patients treated with metformin and placebo. The incidences of pre-specified gastrointestinal adverse experiences in patients treated with the combination of sitagliptin and metformin were similar to those reported for patients treated with metformin alone. See Table 2.

Table 2 Hypoglycaemia and Pre-specified Gastrointestinal Adverse Experiences (Regardless of Investigator Assessment of Causality) Reported in Patients Receiving Combination Therapy[†]

	Number of Patients (%)					
	Study of Sitagliptin and Metformin as Initial Therapy				Study of Sitagliptin as Add-on to Metformin	
	Placebo	Sitagliptin 100 mg q.d.	Metformin 500 or 1000 mg b.i.d. ^{††}	Sitagliptin 50 mg b.i.d. + Metformin 500 or 1000 mg b.i.d. ^{††}	Placebo and Metformin ≥1500 mg daily	Sitagliptin 100 mg q.d. and Metformin ≥1500 mg daily
	N = 176	N = 179	N = 364	N = 372	N= 237	N= 464
Hypoglycaemia	1 (0.6)	1 (0.6)	3 (0.8)	6 (1.6)	5 (2.1)	6 (1.3)
Diarrhoea	7 (4.0)	5 (2.8)	28 (7.7)	28 (7.5)	6 (2.5)	11 (2.4)
Nausea	2 (1.1)	2 (1.1)	20 (5.5)	18 (4.8)	2 (0.8)	6 (1.3)
Vomiting	1 (0.6)	0 (0.0)	2 (0.5)	8 (2.1)	2 (0.8)	5 (1.1)
Abdominal Pain [†]	4 (2.3)	6 (3.4)	14 (3.8)	11 (3.0)	9 (3.8)	10 (2.2)

[†] In the study of initial therapy, Abdominal Discomfort was included with Abdominal Pain
^{††} Data pooled for the patients given the lower and higher doses of metformin.

In all studies, adverse experiences of hypoglycaemia were based on all reports of symptomatic hypoglycaemia; a concurrent glucose measurement was not required.

Sitagliptin in combination with metformin and a sulfonylurea

In a 24-week placebo-controlled study of sitagliptin 100 mg daily added to ongoing combination treatment with glimepiride ≥ 4 mg daily and metformin ≥ 1500 mg daily, the medicine-related adverse reactions reported in ≥ 1% of patients treated with sitagliptin (N=116) and more commonly than in patients treated with placebo (N=113) were hypoglycaemia (sitagliptin, 13.8%; placebo, 0.9%) and constipation (1.7%, 0.0%).

Sitagliptin in combination with metformin and insulin

In a 24 week placebo-controlled study of sitagliptin 100 mg added to ongoing combination treatment with metformin ≥ 1500 mg daily and insulin, the only drug-related adverse reaction reported in ≥ 1% of patients treated with sitagliptin (N=229) and more commonly than in patients treated with placebo (N=233) was hypoglycaemia (sitagliptin, 10.9%; placebo, 5.2%). In another 24-week study of patients receiving sitagliptin as add-on therapy while undergoing insulin intensification (with or without metformin), the only drug-related adverse reaction reported in ≥1% in patients treated with sitagliptin and metformin and more commonly than in patients treated with placebo and metformin was vomiting (sitagliptin and metformin, 1.1%; placebo and metformin, 0.4%).

Pancreatitis

In a pooled analysis of 19 double-blind clinical trials that included data from 10,246 patients randomised to receive sitagliptin 100 mg/day (N=5429) or corresponding (active or placebo) control (N=4817), the incidence of non-adjudicated acute pancreatitis events was 0.1 per 100 patient-years in each group (4 patients with an event in 4708 patient-years for sitagliptin and 4 patients with an event in 3942 patient-years for control) See also TECOS Cardiovascular Safety Study, below. (See 4.4 Special warnings and precautions for use, Pancreatitis).

With the combination of sitagliptin and metformin, no clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed.

Established adverse reactions with sitagliptin

There were no medicine-related adverse reactions reported that occurred with an incidence of $\geq 1\%$ in patients receiving sitagliptin.

Established adverse reactions with metformin

The most common adverse experiences due to initiation of metformin therapy are diarrhoea, nausea, vomiting, gastrointestinal upsets, and metallic taste.

TECOS Cardiovascular safety study

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7,332 patients treated with sitagliptin, 100 mg daily (or 50 mg daily if the baseline estimated glomerular filtration rate (eGFR) was ≥ 30 and < 50 mL/min/1.73 m²), and 7,339 patients treated with placebo in the intention-to-treat population. Both treatments were added to usual care targeting regional standards for HbA1c and CV risk factors. The study population included a total of 2,004 patients ≥ 75 years of age (970 treated with sitagliptin and 1,034 treated with placebo). The overall incidence of serious adverse events in patients receiving sitagliptin was similar to that in patients receiving placebo. Assessment of pre-specified diabetes-related complications revealed similar incidences between groups including infections (18.4% of the sitagliptin-treated patients and 17.7% of the placebo-treated patients) and renal failure (1.4% of sitagliptin-treated patients and 1.5% of placebo-treated patients). The adverse event profile in patients ≥ 75 years of age was generally similar to the overall population.

In the intention-to-treat population, among patients who were using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycaemia was 2.7% in sitagliptin-treated patients and 2.5% in placebo-treated patients; among patients who were not using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycaemia was 1.0% in sitagliptin-treated patients and 0.7% in placebo-treated patients. The incidence of adjudication-confirmed pancreatitis events was 0.3% in sitagliptin-treated patients and 0.2% in placebo-treated patients. The incidence of adjudication-confirmed malignancy events was 3.7% in sitagliptin treated patients and 4.0% in placebo-treated patients.

Postmarketing experience

Additional adverse reactions have been identified during postmarketing use of JANUMET or sitagliptin, one of the components of JANUMET. These reactions have been reported when JANUMET or sitagliptin have been used alone and/or in combination with other anti-hyperglycaemic agents. 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.

Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome (see 4.3 Contraindications and 4.4 Special warnings and precautions for use, Sitagliptin phosphate, Hypersensitivity Reactions); acute pancreatitis, including fatal and non-fatal haemorrhagic and necrotising pancreatitis (see Warnings and Precautions, Pancreatitis); worsening renal function, including acute renal failure (sometimes requiring dialysis); bullous pemphigoid (see Special warnings and precautions for use, Bullous pemphigoid); upper respiratory tract infection; nasopharyngitis; constipation; vomiting; headache; arthralgia; myalgia; pain in extremity; back pain; pruritus.

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/microL difference in WBC vs placebo; mean baseline WBC approximately 6600 cells/microL) 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 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, is, however, very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B₁₂ supplementation (see 4.4 Special warnings and precautions for use, *Metformin hydrochloride*).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

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 5.1 Pharmacodynamics properties, Cardiac Electrophysiology). There is no experience with doses above 800 mg in clinical studies. 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 periods of up to 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 4.4 Special warnings and precautions for use, *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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Combinations of oral blood glucose lowering drugs, ATC code: A10BD07.

JANUMET

JANUMET combines two anti-hyperglycaemic 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 a member of a class of oral anti-hyperglycaemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors, which improve glycaemic control in patients with type 2 diabetes by enhancing the levels of active incretin hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. 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 by intracellular signalling pathways involving cyclic AMP. Treatment with GLP-1 or with DPP-4 inhibitors in animal models of type 2 diabetes has been demonstrated to improve beta cell responsiveness to glucose and stimulate insulin biosynthesis and release. With higher insulin levels, tissue glucose uptake is enhanced. In addition, GLP-1 lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon concentrations, along with higher insulin levels, lead to reduced hepatic glucose production, resulting in a decrease in blood glucose levels. The effects of GLP-1 and GIP are glucose-dependent such that when blood glucose concentrations are low, stimulation of insulin release and suppression of glucagon secretion by GLP-1 are not observed. For both GLP-1 and GIP, stimulation of insulin release is enhanced as glucose rises above normal concentrations. Further, GLP-1 does not impair the normal glucagon response to hypoglycaemia. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyses the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in a glucose-dependent manner. In patients with type 2 diabetes with hyperglycaemia, these changes in insulin and glucagon levels lead to lower haemoglobin A_{1c} (HbA_{1c}) and lower fasting and postprandial glucose concentrations. The glucose-dependent mechanism of sitagliptin is distinct from the mechanism of sulfonylureas, which increases insulin secretion even when glucose levels are low and can lead to hypoglycaemia in patients with type 2 diabetes and in normal subjects. Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations.

Metformin hydrochloride

Metformin is an anti-hyperglycaemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral anti-hyperglycaemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilisation. Unlike sulfonylureas, metformin does not produce hypoglycaemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see 4.4 Special warnings and precautions for use, *Metformin hydrochloride*) and does not cause hyperinsulinaemia.

With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

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 two-day study in healthy adult subjects, the effects on post-meal plasma concentrations of active and total GLP-1 and glucose after coadministration of sitagliptin and metformin were compared with those after administration of sitagliptin alone, metformin alone or placebo, each administered for two 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 coadministration 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 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), coadministration 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 postdose 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.

5.2 Pharmacokinetic properties

JANUMET

The results of a definitive bioequivalence study in healthy subjects demonstrated that the JANUMET (sitagliptin/metformin hydrochloride) 50 mg/500 mg and 50 mg/1000 mg combination tablets are bioequivalent to coadministration of corresponding doses of sitagliptin phosphate (JANUVIA) and metformin hydrochloride as individual tablets.

Because bioequivalence is demonstrated at the lowest and highest combination tablet dose strengths available, bioequivalence is conferred to the (sitagliptin/metformin) 50 mg/850 mg fixed dose combination (FDC) tablet.

Absorption

Sitagliptin phosphate

The absolute bioavailability of sitagliptin is approximately 87%. Coadministration 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 50-60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1500 mg, and 850 mg to 2550 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 sulfonylureas, 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 24-48 hours and are generally < 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, cyclosporine, 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.

Characteristics in patients

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 impairment

Sitagliptin phosphate

An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal impairment with eGFR of 30 to $<45 \text{ mL/min/1.73 m}^2$, and an approximately 4-fold increase was observed in patients with severe renal impairment (eGFR $< 30 \text{ mL/min/1.73 m}^2$) including patients with ESRD on haemodialysis, as compared to subjects with normal renal function.

Metformin hydrochloride

In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased (see 4.3 Contraindications and 4.4 Special warnings and precautions for use).

Hepatic impairment

Sitagliptin phosphate

In patients with moderate hepatic impairment (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 impairment (Child-Pugh score > 9). However, because sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetics of sitagliptin.

Metformin hydrochloride

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

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 anti-hyperglycaemic 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.

Paediatric patients

No studies with JANUMET have been performed in paediatric patients.

Race

Sitagliptin phosphate

Race 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, including subjects of white, Hispanic, black, Asian, and other racial groups.

Metformin hydrochloride

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes, the anti-hyperglycaemic effect was comparable in whites (n=249), blacks (n= 51), and Hispanics (n=24).

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.

5.3 Preclinical safety data

Acute toxicity

Sitagliptin phosphate

The approximate LD50 of sitagliptin given orally to rats is > 3000 mg/kg (maximum dose tested). This dose is equivalent to ≥ 200 times the human exposure based on the recommended daily adult human dose of 100 mg/day. In mice the approximate oral LD50 of sitagliptin is 4000 mg/kg. This dose is equivalent to > 385 times the human exposure based on recommended daily adult human dose of 100 mg/day.

Chronic toxicity

Sitagliptin and metformin

Preclinical toxicokinetic and oral toxicity studies in dogs have been conducted with the combined products in JANUMET.

In a sixteen-week oral toxicity study, female dogs were administered 20 mg/kg/day of metformin, alone or in combination with 2, 10, or 50 mg/kg/day of sitagliptin. Transient ataxia and/or tremors were observed in the high-dose combination-treatment group. These signs were considered to be an effect of sitagliptin because they were seen in previous dog studies with sitagliptin alone at 50 mg/kg/day. The no-effect level for treatment-related changes in this study was 10 mg/kg/day of sitagliptin plus 20 mg/kg/day of metformin, which provided systemic exposure to sitagliptin of approximately 6 times that in patients treated with 100 mg/day of sitagliptin and systemic exposure to metformin of approximately 2.5 times that in patients treated with 2000 mg/day of metformin.

Sitagliptin phosphate

The toxicity potential of sitagliptin was evaluated in a series of repeated dose toxicity studies of up to 53 weeks in dogs and up to 27 weeks in rats. In dogs administered sitagliptin orally at dosages of 2, 10 and 50 mg/kg/day, the no-observed effect level was 10 mg/kg/day (up to 6 times the human exposure based on the recommended daily adult human dose of 100 mg/day). Treatment-related physical signs observed in the 50-mg/kg/day group included open-mouth breathing, salivation, white foamy emesis, ataxia, trembling, decreased activity, and/or hunched posture. These signs were transient, slight in degree, and occurred with decreased incidence during the course of the study. In addition, very slight to slight skeletal muscle degeneration was observed histologically in the 14- and 27-week toxicity studies at the 50-mg/kg/day dose. However, no skeletal muscle degeneration was found in the 53-week toxicity study, indicating the lack of reproducibility or progression of this change with increased duration of treatment. The 50-mg/kg/day dose in dogs resulted in systemic exposure values 26 times the human exposure at the recommended daily adult human dose of 100 mg/day.

In rats, sitagliptin administered orally at dosages of up to 180 mg/kg/day (up to 23 times the human exposure based on the recommended daily adult human dose of 100 mg/day), no significant toxicity was observed. The only medicine-related effect observed was post-dose salivation, likely related to poor palatability of the medicine, at doses of 60 mg/kg/day and 180 mg/kg/day.

The treatment-related changes noted in animals are not considered to have any clinical impact at the recommended therapeutic dosages in humans.

Carcinogenicity

Sitagliptin phosphate

A two-year carcinogenicity study was conducted in male and female rats given oral doses of sitagliptin of 50, 150, and 500 mg/kg/day. There was an increased incidence of hepatic adenomas and carcinomas in the high-dose males and hepatic carcinomas in the high-dose females. This dose in rats results in approximately 58 times the human exposure based on the recommended daily adult human dose of 100 mg/day. This dose level was associated with hepatotoxicity in rats. The no-observed effect level for induction of hepatic neoplasia was 150 mg/kg/day, approximately 19-fold the human exposure at the 100-mg recommended dose. Since hepatotoxicity has been shown to correlate with induction of hepatic neoplasia in rats, this increased incidence of hepatic tumours in rats was likely secondary to chronic hepatic toxicity at this high dose. The clinical significance of these findings for humans is unknown.

A two-year carcinogenicity study was conducted in male and female mice at oral doses of 50, 125, 250, and 500 mg/kg/day. Sitagliptin did not increase tumour incidence in mice in any organ at doses up to 500 mg/kg/day (approximately 68 times the human exposure based on the recommended daily adult human dose of 100 mg/day).

Metformin hydrochloride

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

Mutagenesis

Sitagliptin phosphate

Sitagliptin was not mutagenic or clastogenic in a battery of genetic toxicology studies, including the Ames bacterial assay (microbial mutagenesis test), Chinese hamster ovary cells (CHO cells) chromosome aberration assay, an in vitro cytogenetics assay using CHO cells, an in vitro rat hepatocyte DNA alkaline elution assay (an assay which measures the compound's ability to induce single strand breaks in DNA), and an *in vivo* micronucleus assay.

Metformin hydrochloride

There was no evidence of a mutagenic potential of metformin in the following in vitro tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Reproduction

Sitagliptin phosphate

No adverse effects upon fertility were observed in male and female rats given sitagliptin orally at doses up to 1000 mg/kg daily (up to approximately 100 times the human exposure based on the recommended daily adult human dose of 100 mg/day) prior to and throughout mating.

Metformin hydrochloride

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

Development

Sitagliptin phosphate

Sitagliptin was not teratogenic in rats at oral doses up to 250 mg/kg or in rabbits given up to 125 mg/kg during organogenesis (up to 32 and 22 times the human exposure based on the recommended daily adult human dose of 100 mg/day). A slight, treatment-related increased incidence of foetal rib malformations (absent, hypoplastic and wavy ribs) was observed in the offspring of rats at oral doses of 1000 mg/kg/day (approximately 100 times the human exposure based on the recommended daily adult human dose of 100 mg/day). The no-observed effect level for developmental effects was 250 mg/kg/day (32 times the human exposure based on the recommended daily adult human dose of 100 mg/day). Treatment-related decreases in the mean preweaning body weight of both sexes and postweaning body weight gain of male animals was observed in offspring of rats at oral doses of 1000 mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each film-coated tablet of JANUMET contains the following inactive ingredients: microcrystalline cellulose, polyvinylpyrrolidone, sodium lauryl sulfate, 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.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25°C (77°F).

6.5 Nature and contents of container

Opaque blisters (aluminium/aluminium or PVDC/aluminium). Packs of 14 or 56 tablets.

Not all presentations are available.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Further Information

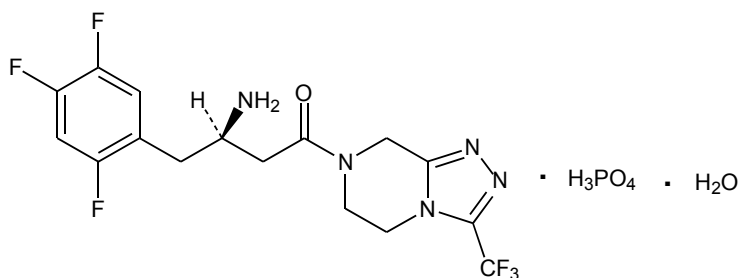
Chemistry

JANUMET contains sitagliptin phosphate and metformin hydrochloride.

Sitagliptin phosphate

The chemical name of sitagliptin phosphate is 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyrazine phosphate (1:1) monohydrate.

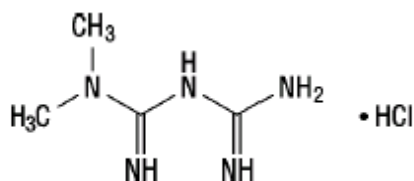
The empirical formula is $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and the molecular weight is 523.32. The structural formula is:



Sitagliptin phosphate monohydrate is a white to off-white, crystalline, non-hygroscopic powder. It is soluble in water and N,N-dimethyl formamide; slightly soluble in methanol; very slightly soluble in ethanol, acetone, and acetonitrile; and insoluble in isopropanol and isopropyl acetate.

Metformin hydrochloride

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral anti-hyperglycaemic agents. The structural formula is as shown:



Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

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NEW ZEALAND

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9. DATE OF FIRST APPROVAL

5 March 2009

10. DATE OF REVISION OF THE TEXT

5 April 2018

11. SUMMARY TABLE OF CHANGES

Date	Change
April 2018	<p>4.2 Dose and method of administration, revised dosing recommendations for use in patients with renal impairment based on eGFR ranges; and addition of dosing recommendation for the discontinuation of JANUMET prior to an iodinated contrast imaging procedure.</p> <p>4.3 Contraindication, revised contraindication from renal disease or dysfunction to severe renal impairment with eGFR <30mL/min/1.73m²</p> <p>4.4 Special warnings and precautions for use: revised precautionary text for use in patients with renal impairment based on eGFR ranges.</p> <p>Revised Metformin hydrochloride, lactic acidosis text with the deletion of text regarding initiation of metformin in patients ≥80 years of age.</p> <p>Revised section on Radiological studies involving use of intravascular iodinated contrast materials, with additional text for risk factors for lactic acidosis.</p> <p>Revised text for Use in the elderly, with deletion of text relating to the use of metformin in only those patients with normal renal function.</p> <p>4.5 Interaction with other medicines and other forms of interaction, revised text regarding drug interactions with cationic drugs.</p> <p>4.8 Undesirable effects, addition of 'Reporting of suspected adverse reactions' statement.</p> <p>5.2 Pharmacokinetic properties- Characteristics in patients: added eGFR ranges to define moderate and severe renal impairment; and revised Elderly: Metformin hydrochloride section with deletion of text regarding use of metformin in patients ≥ 80 years of age.</p>

S-WPC-MK0431-T-052017 and 052017a