

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

PRODUCT INFORMATION

JANUMET®

(sitagliptin phosphate monohydrate/metformin hydrochloride, MSD)

50 mg/500 mg, 50 mg/850 mg & 50 mg/1000 mg

DESCRIPTION

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

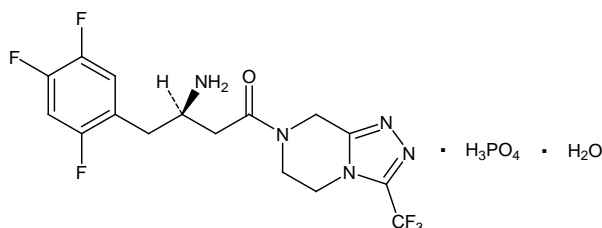
JANUMET is available for oral administration as film-coated tablets containing sitagliptin phosphate monohydrate and metformin hydrochloride equivalent to: 50 mg sitagliptin as free base and 500 mg metformin hydrochloride (JANUMET 50 mg/500 mg), 850 mg metformin hydrochloride (JANUMET 50 mg/850 mg) or 1000 mg metformin hydrochloride (JANUMET 50 mg/1000 mg).

Each film-coated tablet of JANUMET contains the following inactive ingredients: microcrystalline cellulose, povidone, sodium lauryl sulfate, and sodium stearyl fumarate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, macrogol 3350, talc purified, titanium dioxide, iron oxide red CI77491, and iron oxide black CI77499.

Sitagliptin phosphate monohydrate

The chemical name of sitagliptin phosphate monohydrate 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 CAS Registry Number is 654671-77-9.

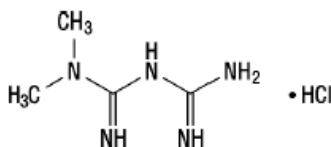
The empirical formula is $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and the molecular weight is 523.32. The structural formula is:



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. The pKa of sitagliptin is 7.7

Metformin hydrochloride

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycaemic agents. The CAS Registry Number is 1115-70-4. The structural formula is as shown:



Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

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 pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

PHARMACOLOGY

Mechanism of Action

Sitagliptin phosphate monohydrate

Sitagliptin phosphate monohydrate is a member of a class of oral antihyperglycaemic 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 insulintropic 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. This glucose-dependent mechanism is unlike the mechanism seen with sulfonylureas, whereby insulin is released even when glucose levels are low and can lead to hypoglycaemia in patients with type 2 diabetes and in normal subjects. 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. Sitagliptin inhibits DPP-4 with nanomolar potency (IC_{50} 18 nM). It does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations. Inhibition of DPP-8 or DPP-9 is associated with toxicity in preclinical animal models and alteration of immune function *in vitro*.

Metformin hydrochloride

Metformin is an antihyperglycaemic 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 antihyperglycaemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycaemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see **PRECAUTIONS**, *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.

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

Pharmacokinetics

The results of a definitive bioequivalence study in healthy subjects demonstrated that the JANUMET (sitagliptin phosphate monohydrate/metformin hydrochloride) 50 mg/500 mg and 50 mg/1000 mg combination tablets are bioequivalent to co-administration of corresponding doses of sitagliptin phosphate monohydrate (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 monohydrate

The absolute bioavailability of sitagliptin is approximately 87%. Co-administration of a high-fat meal 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 alteration 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 monohydrate

The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 liters. 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 monohydrate

Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79% of sitagliptin is excreted unchanged in the urine.

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

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) or biliary excretion.

Elimination

Sitagliptin phosphate monohydrate

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, cyclosporin, 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 drug 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 monohydrate

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

JANUMET should not be used in patients with renal insufficiency (see **CONTRAINDICATIONS**).

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

Sitagliptin phosphate monohydrate

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 monohydrate

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. 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 monohydrate

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 monohydrate

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

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see **GLUCOPHAGE**¹ US prescribing information: **CLINICAL PHARMACOLOGY**, Special Populations, Geriatrics).

JANUMET treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced (see **PRECAUTIONS**, *Metformin hydrochloride*).

Paediatric

No studies with JANUMET have been performed in paediatric patients.

Race

Sitagliptin phosphate monohydrate

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 antihyperglycaemic effect was comparable in whites (n=249), blacks (n= 51), and Hispanics (n=24).

Body Mass Index (BMI)

Sitagliptin phosphate monohydrate

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.

Pharmacodynamics

Sitagliptin phosphate monohydrate

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.

¹ **GLUCOPHAGE**® in the US is a registered trademark of Merck Sante S.A.S, an associate of Merck KGaA of Darmstadt, Germany. Licensed to Bristol-Meyers Squibb Company.

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

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 co-administration 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 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 or cause hypoglycaemia, suggesting that the insulinotropic and glucagon suppressive actions of the drug are glucose dependent.

Effects on blood pressure

In a randomised, placebo-controlled crossover study in hypertensive patients on one or more anti-hypertensive drugs (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 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.

Clinical Studies

Clinical studies of the co-administration of sitagliptin and metformin demonstrated significant improvements in glycaemic control in patients with type 2 diabetes. There have been no clinical efficacy studies conducted with JANUMET tablets; however, bioequivalence of JANUMET tablets with co-administered sitagliptin and metformin hydrochloride tablets was demonstrated.

Sitagliptin and Metformin as Initial Therapy in Patients with Type 2 Diabetes

This study consisted of a 24-week, placebo-controlled Phase A, a 30-week, active-controlled Phase B, and a 50-week active-controlled Extension Phase, where 1091 patients with type 2 diabetes and inadequate glycaemic control on diet and exercise were enrolled in a randomized,

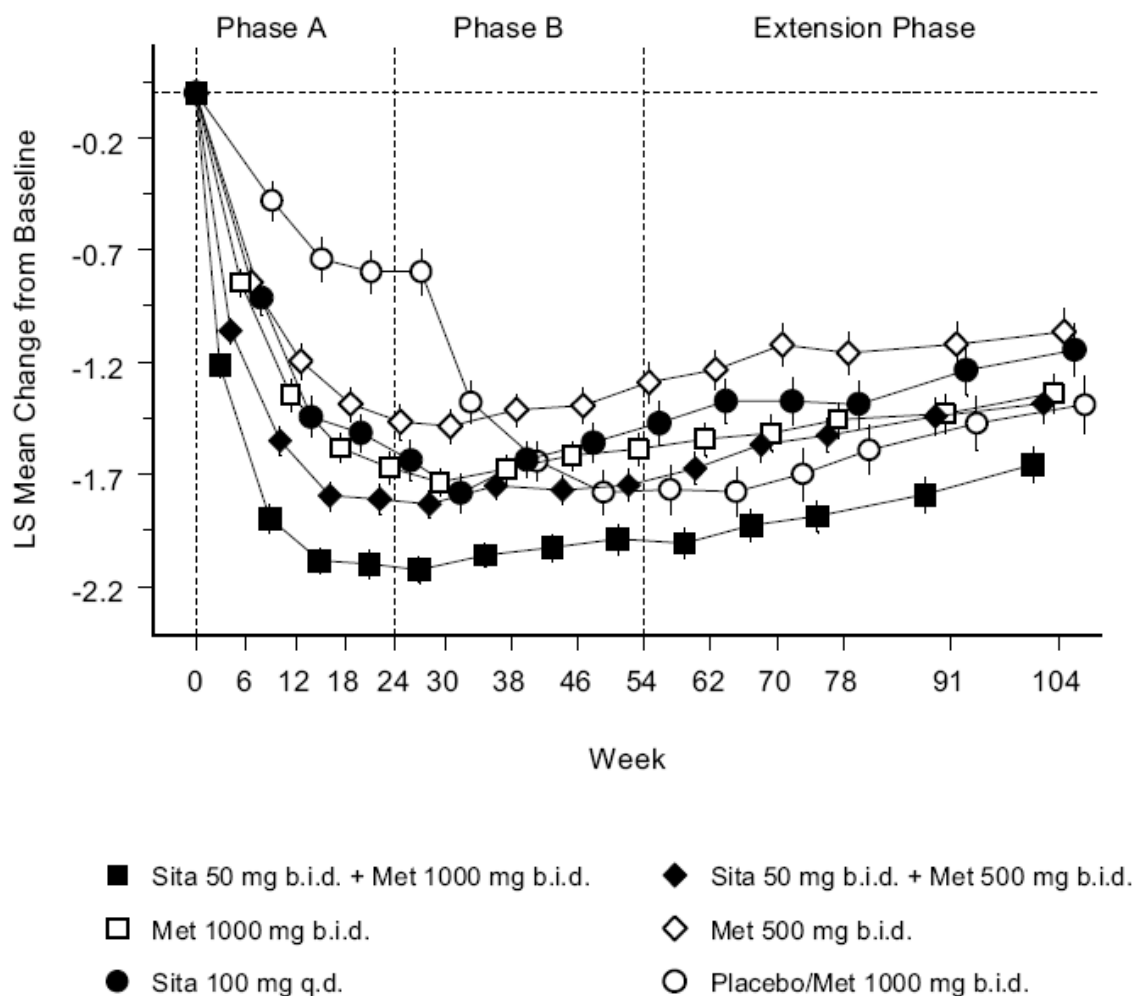
Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

double-blind, parallel-group factorial study designed to assess the safety and efficacy of initial therapy with the combination of sitagliptin and metformin. Patients on an antihyperglycaemic agent (N=541) underwent a diet, exercise, and drug washout period of up to 12 weeks duration. After the washout period, patients with inadequate glycaemic control (A_{1c} 7.5% to 11%) were randomized after completing a 2-week single-blind placebo run-in period. Patients not on antihyperglycaemic agents at study entry (N=550) with inadequate glycaemic control (A_{1c} 7.5% to 11%) immediately entered the 2-week single-blind placebo run-in period and then were randomized. A total of 685 patients entered the 50-week extension study, and among these patients, 517 (74.5%) completed the study. Approximately equal numbers of patients were randomized to receive initial therapy with placebo; 100 mg of sitagliptin once daily; 500 mg or 1000 mg of metformin twice daily; or 50 mg of sitagliptin twice daily in combination with 500 mg or 1000 mg of metformin twice daily. Patients receiving active therapy continued with their assigned treatment regimen until the end of the study, unless rescue (glibenclamide) was required. Patients receiving placebo were switched to 1000 mg of metformin twice daily at the beginning of Phase B.

Initial combination therapy with sitagliptin 100 mg and metformin 1000 mg or 2000 mg daily provided sustained improvements in HbA_{1c} and FPG and 2-hour PPG compared with either corresponding monotherapy dose over 104 weeks ; (Table 1, Figure 1). An improvement in FPG, with near maximal FPG reduction, was achieved by the 3-week time point (the first time point assessed after initiation of therapy) and sustained over time. A slight upward trend in the reduction in HbA_{1c} was observed during the extension phase in each treatment group. Measures of beta cell function, HOMA- β and the proinsulin to insulin ratio generally showed greater improvement with the co-administration of sitagliptin and metformin compared with either monotherapy alone. Lipid effects were generally neutral. The decrease in body weight in the groups given sitagliptin in combination with metformin was similar to that in the groups given metformin alone or placebo. Mean reductions from baseline in HbA_{1c} compared with placebo were generally greater for patients with higher baseline HbA_{1c} values. The improvement in HbA_{1c} was generally consistent across subgroups defined by gender, age, race, or baseline BMI. Mean reductions from baseline in HbA_{1c} for patients not on an antihyperglycaemic agent at study entry were: sitagliptin 100 mg once daily, -1.14%; metformin 500 mg bid, -1.20%; metformin 1000 mg bid, -1.22%; sitagliptin 50 mg bid with metformin 500 mg bid, -1.65%; and sitagliptin 50 mg bid with metformin 1000 mg bid, -1.74%; and for patients receiving placebo/metformin, -1.11%.

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

Figure 1: Mean Change from Baseline for HbA_{1c} over 104 Weeks with Sitagliptin and Metformin, Alone and in Combination as Initial Therapy in Patients with Type 2 Diabetes*



* Statistical comparisons apply only to Phase A - formal statistical comparisons are not possible for Phase B and the extension phase.

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

Table 1
Glycaemic Parameters and Body Weight at Final Visit (24-Week Study)
for Sitagliptin and Metformin, Alone and in Combination as Initial Therapy[†]

	Placebo	Sitagliptin 100 mg q.d.	Metformin 500 mg b.i.d.	Sitagliptin 50 mg b.i.d. + Metformin 500 mg b.i.d.	Metformin 1000 mg b.i.d.	Sitagliptin 50 mg b.i.d. + Metformin 1000 mg b.i.d.
HbA_{1c} (%)[‡]	N = 165	N = 175	N = 178	N = 183	N = 177	N = 178
Baseline (mean)	8.68	8.87	8.90	8.79	8.68	8.76
Change from baseline (adjusted mean [‡])	0.17	-0.66	-0.82	-1.40	-1.13	-1.90
Difference from placebo (adjusted mean [‡])	-	-0.83 [§]	-0.99 [§]	-1.57 [§]	-1.30 [§]	-2.07 [§]
Patients (%) achieving HbA _{1c} <7%	15 (9.1)	35 (20.0)	41 (23.0)	79 (43.2)	68 (38.4)	118 (66.3)
% Patients receiving rescue medication	32	21	17	8	12	2
FPG (mmol/L)[‡]	N = 169	N = 178	N = 179	N = 183	N = 179	N = 180
Baseline (mean)	10.90	11.18	11.39	11.32	10.94	10.92
Change from baseline (adjusted mean [‡])	0.32	-0.97	-1.52	-2.61	-1.63	-3.55
Difference from placebo (adjusted mean [‡])	-	-1.29 [§]	-1.84 [§]	-2.94 [§]	-1.95 [§]	-3.87 [§]
2-hour PPG (mmol/L)[‡]	N = 129	N = 136	N = 141	N = 147	N = 138	N = 152
Baseline (mean)	15.37	15.84	16.25	16.20	15.73	15.93
Change from baseline (adjusted mean [‡])	0.02	-2.88	-2.96	-5.13	-4.33	-6.47
Difference from placebo (adjusted mean [‡])	-	-2.90 [§]	-2.98 [§]	-5.15 [§]	-4.35 [§]	-6.49 [§]
Body Weight (kg)[%]	N = 167	N = 175	N = 179	N = 184	N = 175	N = 178
Baseline (mean)	90.1	85.9	88.1	90.0	89.4	88.2
Change from baseline (adjusted mean [‡])	-0.9	0.0	-0.9	-0.6	-1.1	-1.3
Difference from placebo (adjusted mean [‡])	-	0.9 [¶]	0.1 [#]	0.4 [#]	-0.1 [#]	-0.3 [#]

[†] All Patients Treated Population (an intention-to-treat analysis).

[‡] Least squares means adjusted for prior antihyperglycaemic therapy status and baseline value.

[§] p<0.001 compared to placebo.

[%] All Patients as Treated (APaT) population, excluding patients given glycaemic rescue therapy.

[¶] p=0.005 compared to placebo.

[#] Not statistically significant (p≥0.05) compared to placebo.

[‡] Primary efficacy outcome

[‡] Secondary efficacy outcome

In addition, this study included patients (N=117) with more severe hyperglycaemia (HbA_{1c} >11% or blood glucose >15.54 mmol/L) who were treated with open-label sitagliptin at 50 mg and metformin at 1000 mg twice daily for 24 weeks, but were not eligible to enter Phase B of the study. In this group of patients, the baseline HbA_{1c} value was 11.15%, FPG was 17.45 mmol/L, and 2-hour PPG was 24.48 mmol/L. After 24 weeks, decreases from baseline of -2.94 % for HbA_{1c}, -7.03 mmol/L for FPG, and -11.54 mmol/L for 2-hour PPG were observed. In this open-label cohort, a modest increase in body weight of 1.3 kg was observed at 24 weeks.

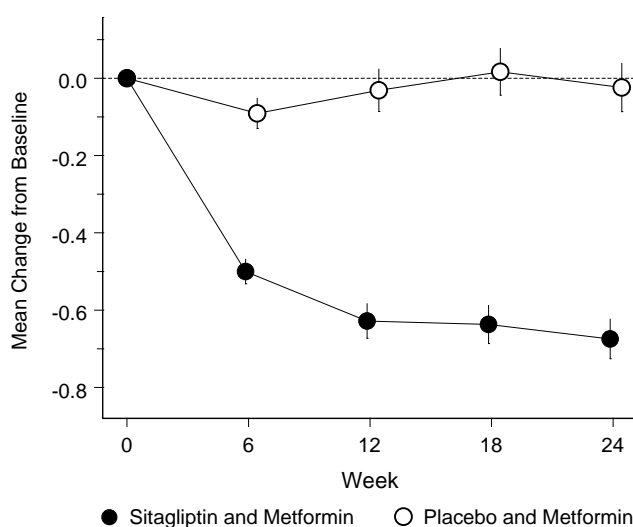
Sitagliptin Add-on Therapy in Patients Inadequately Controlled on Metformin Alone:

The combination of sitagliptin and metformin has been evaluated for safety and efficacy in two double-blind, placebo-controlled clinical studies in patients with type 2 diabetes mellitus. In both studies, patients with inadequate glycaemic control on stable doses of metformin ≥1500 mg were randomised to receive either sitagliptin 100 mg per day or placebo in addition to ongoing treatment with metformin.

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

In one study, 701 patients received 100 mg of sitagliptin or placebo once daily for 24 weeks. This study used the reduction from baseline in haemoglobin A1c (HbA_{1c}) as the primary outcome variable. Pre-specified secondary endpoints included FPG and 2-hour PPG. The addition of sitagliptin to ongoing metformin treatment provided significant improvements compared with the addition of placebo to ongoing metformin treatment in HbA_{1c} (-0.65%), FPG (-1.41 mmol/L), and 2-hour PPG (-2.81 mmol/L) (see Figure 1 and Table 1). This improvement in HbA_{1c} compared to placebo was not affected by baseline HbA_{1c} value, prior antihyperglycaemic therapy, gender, age, baseline BMI, length of time since diagnosis of diabetes, presence of metabolic syndrome, or standard indices of insulin resistance (HOMA-IR) or insulin secretion (HOMA-β). Compared to patients taking placebo, patients taking sitagliptin demonstrated slight decreases in total cholesterol, non-HDL cholesterol and triglycerides. A similar decrease in body weight was observed for both treatment groups.

Figure 2: Mean Change from Baseline for HbA_{1c} (%) over 24 Weeks with Sitagliptin 100-mg Total Daily Dose added to Metformin (≥ 1500 mg) or Placebo added to Metformin (≥ 1500 mg) in Patients with Type 2 Diabetes^{†‡}



[†] Patients with inadequate glycaemic control on metformin monotherapy.

[‡] All Patients Treated Population Least squares means adjusted for prior antihyperglycaemic therapy and baseline value.

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

**Table 2: Glycaemic Parameters and Body Weight at Final Visit (24-Week Study)
Sitagliptin as Add-on Therapy in Patients with
Inadequate Glycaemic Control on Metformin[†]**

	Sitagliptin 100 mg once daily + Metformin	Placebo + Metformin
HbA_{1c} (%)	N = 453	N = 224
Baseline (mean)	7.96	8.03
Change from baseline (adjusted mean [‡])	-0.67	-0.02
Difference from placebo + metformin (adjusted mean [‡])	-0.65 [§]	
Patients (%) achieving HbA _{1c} <7%	213 (47.0)	41 (18.3)
FPG (mmol/L)	N = 454	N = 226
Baseline (mean)	9.44	9.63
Change from baseline (adjusted mean [‡])	-0.94	0.47
Difference from placebo + metformin (adjusted mean [‡])	-1.41 [§]	
2-hour PPG (mmol/L)	N = 387	N = 182
Baseline (mean)	15.24	15.12
Change from baseline (adjusted mean [‡])	-3.44	-0.63
Difference from placebo + metformin (adjusted mean [‡])	-2.81 [§]	
Body Weight (kg)	N = 399	N = 169
Baseline (mean)	86.9	87.6
Change from baseline (adjusted mean [‡])	-0.7	-0.6
Difference from placebo + metformin (adjusted mean [‡])	-0.1 [¶]	

[†] All Patients Treated Population (an intention-to-treat analysis).

[‡] Least squares means adjusted for prior antihyperglycaemic therapy and baseline value.

[§] p<0.001 compared to placebo + metformin.

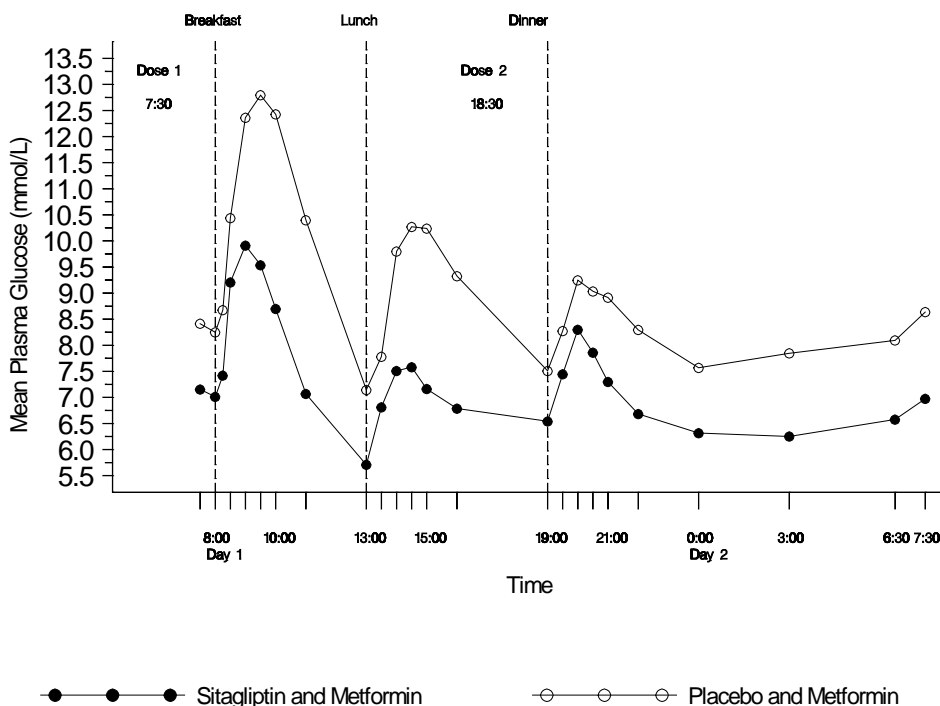
^{||} All Patients as Treated (APaT) population, excluding patients given glycaemic rescue therapy.

[¶] Not statistically significant (p≥0.05) compared to placebo + metformin.

In a separate study, 24-hour plasma glucose values were assessed. This study used the reduction in 24-hour weighted mean glucose (WMG) as the primary outcome variable. Twenty-eight patients received either 50 mg sitagliptin or placebo twice daily for 4 weeks in addition to their twice daily metformin regimen. Following 4 weeks of treatment, the difference in glucose lowering efficacy was assessed as WMG based upon collection of multiple blood samples, including those obtained before and after meals as well as overnight. Sitagliptin 50 mg co-administered twice daily with metformin significantly lowered the 24-hour WMG (-1.82 mmol/L) compared to placebo co-administered with metformin. In addition, sitagliptin administered with metformin, compared with placebo administered with metformin, substantially lowered fasting glucose concentrations and demonstrated smaller glucose excursions after all three meals (see Figure 2). In patient-collected glucose measurements, treatment with sitagliptin administered with metformin also provided significant reductions compared to placebo administered with metformin in mean fasting plasma glucose (-1.13 mmol/L), 7-point glucose average (-1.55 mmol/L), and 2 hour post-glucose concentrations (-2.03 mmol/L).

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

Figure 3: 24-hour Plasma Glucose Profile after 4-Week Treatment with Sitagliptin 50-mg Twice Daily and Metformin (≥ 1500 mg) or Placebo and Metformin (≥ 1500 mg) in Patients with Type 2 Diabetes[†]



[†]Patients with inadequate glycaemic control on metformin monotherapy.

Active (Glipizide)-Controlled Study in Combination with Metformin

Long-term maintenance of effect was evaluated in a 52-week, double-blind, glipizide-controlled trial in patients with type 2 diabetes and inadequate glycaemic control on metformin monotherapy at ≥ 1500 mg/day. In this study, patients were randomised to the addition of either sitagliptin 100 mg daily (N = 588) or glipizide (N = 584) for 52 weeks. Patients receiving glipizide were given an initial dosage of 5 mg/day and then electively titrated by the investigator to a target FPG of <6.11 mmol/L, without significant hypoglycaemia, over the next 18 weeks. A maximum dosage of 20 mg/day was allowed to optimise glycaemic control. Thereafter, the glipizide dose was to have been kept constant. The mean dose of glipizide after the titration period was 10.3 mg.

Both treatments resulted in a statistically significant improvement in glycaemic control from baseline. After 52 weeks, the reduction from baseline in HbA_{1c} was 0.67% for sitagliptin 100 mg daily and 0.67% for glipizide, confirming comparable efficacy of the two agents. The reduction in FPG was 0.56 mmol/L for sitagliptin and 0.42 mmol/L for glipizide. In a post-hoc analysis, patients with higher baseline HbA_{1c} ($\geq 9\%$) in both groups had greater reductions from baseline in HbA_{1c} (sitagliptin, -1.68%; glipizide, -1.76%). In this study, the proinsulin to insulin ratio, a marker of efficiency of insulin synthesis and release, improved with sitagliptin and deteriorated with glipizide treatment. The incidence of hypoglycaemia in the sitagliptin group (4.9%) was significantly lower than that in the glipizide group (32.0%). Patients treated with sitagliptin exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glipizide (-1.5 kg vs. +1.1 kg).

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

Metformin hydrochloride

The prospective randomised (UKPDS 34) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1000 patient-years) versus diet alone (43.3 events/1000 patient-years), $p=0.0023$, and versus the combined sulfonylurea and insulin monotherapy groups (40.1 events/1000 patient-years), $p=0.0034$.
- a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/1000 patient-years, $p=0.017$.
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1000 patient-years versus diet alone 20.6 events/1000 patient-years ($p=0.011$), and versus the combined sulfonylurea and insulin monotherapy groups 18.9 events/1000 patient-years ($p=0.021$).
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1000 patient-years, diet alone 18 events/1000 patient-years ($p=0.01$).

INDICATIONS

JANUMET is indicated as initial therapy in patients with type 2 diabetes mellitus to improve glycaemic control when diet and exercise do not provide adequate glycaemic control, when dual sitagliptin and metformin therapy is appropriate (i.e. high initial HbA_{1c} levels and poor prospects of response to monotherapy).

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

CONTRAINDICATIONS

JANUMET is contraindicated in patients with:

1. Renal disease or renal dysfunction, e.g., as suggested by serum creatinine levels ≥ 133 micromol/L [males] or ≥ 124 micromol/L [females], or abnormal creatinine clearance (<60 mL/min), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicaemia.
2. Known hypersensitivity to sitagliptin phosphate monohydrate, metformin hydrochloride or any other component of JANUMET (see **PRECAUTIONS**, *Sitagliptin phosphate monohydrate*, Hypersensitivity Reactions and **ADVERSE REACTIONS**, *Postmarketing Experience*).
3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.

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

JANUMET is not currently indicated for use in children below 18 years

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

PRECAUTIONS

JANUMET

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

Pancreatitis: In postmarketing experience there have been reports of acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotising pancreatitis (see **ADVERSE REACTIONS, Postmarketing Experience**), in patients taking sitagliptin. Because these reports are made voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. 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. Thus, patients with creatinine clearance <60 mL/min or 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, 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.

Sitagliptin phosphate monohydrate

Hypoglycaemia: 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. The use of sitagliptin in combination with insulin has not been adequately studied.

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 drug 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 **ADVERSE REACTIONS, Postmarketing Experience**.)

Metformin hydrochloride

Lactic Acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with JANUMET; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

(>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is 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. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking 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 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 hypoxemia, 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 nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. 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 stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug 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 drug 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.

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

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 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 recognize in the elderly, and in people who are taking β -adrenergic blocking drugs.

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 drugs that are eliminated by renal tubular secretion (see **DRUG INTERACTIONS**, *Metformin hydrochloride*), should be used with caution.

Radiological 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 **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 characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotaemia. When such events occur in patients on JANUMET therapy, the drug 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, 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.

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

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 stabilized 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.

Effects on fertility

No studies have been conducted with the combined components of JANUMET to evaluate the effects on fertility.

Sitagliptin phosphate monohydrate

No adverse effects on 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.

Use in Pregnancy (Category C)

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 antihyperglycaemic agents, is not recommended for use in pregnancy.

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

Sitagliptin phosphate monohydrate

Sitagliptin was not teratogenic in rats at oral doses up to 250 mg/kg/day or in rabbits given up to 125 mg/kg/day during organogenesis (up to 32 and 22 times, respectively, the human exposure based on the recommended daily adult human dose of 100 mg). In rats, a slight increase in the incidence of fetal 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). Slight decreases in mean birth weight and preweaning and postweaning body weight gains were observed in the offspring of rats given sitagliptin at an oral dose of 1000 mg/kg/day from gestation day 6 to lactation day 20. However, animal reproduction studies are not always predictive of the human response. Sitagliptin crosses the placenta in rats and rabbits.

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

Metformin hydrochloride

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This dose is about 3 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.

Use in Lactation

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 were excreted in the milk of lactating rats. For sitagliptin, excretion occurred at a milk to plasma ratio of 4:1. Treatment of rats with sitagliptin during pregnancy and lactation caused decreased pup body weight gain (see Use in Pregnancy). It is not known whether sitagliptin is excreted in human milk; some excretion of metformin in human milk has been observed. Therefore, JANUMET should not be used by a woman who is nursing.

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 **PRECAUTIONS**, Monitoring of Renal Function).

Sitagliptin phosphate monohydrate

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

Carcinogenicity

No carcinogenicity studies have been conducted with the combined components of JANUMET.

Sitagliptin phosphate monohydrate

A two-year carcinogenicity study was conducted in rats given oral doses of sitagliptin of 50, 150, and 500 mg/kg/day. There was an increased incidence of preneoplastic lesions (altered hepatic foci) in both sexes at 150 and at 500mg/kg/day, and hepatic adenomas and carcinomas in males and hepatic carcinomas in females at 500 mg/kg/day. Systemic exposure in rats at 500 mg/kg/day is approximately 58 times that of humans at the recommended daily adult dose of 100 mg. 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

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

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.

In a two-year carcinogenicity study conducted in mice, sitagliptin did not increase tumour incidence at oral doses up to 500 mg/kg/day (approximately 68 times human exposure at the clinical 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 tumourigenic 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.

Genotoxicity

Sitagliptin phosphate monohydrate

Sitagliptin was not mutagenic or clastogenic in a battery of genetic toxicology studies, including the Ames bacterial mutagenicity assay, a chromosome aberration assay in Chinese hamster ovary 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* mouse 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.

Interactions with other medicines

Sitagliptin and Metformin

Co-administration 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 drug interaction studies with JANUMET have not been performed; however, such studies have been conducted with the individual components of JANUMET (sitagliptin phosphate monohydrate and metformin hydrochloride).

Sitagliptin phosphate monohydrate

In Vitro Assessment of Drug Interactions

Sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6 at therapeutic concentrations, and is not an inducer of CYP3A4. Sitagliptin is a p-glycoprotein substrate, but does not inhibit p-glycoprotein mediated transport of digoxin. Based on these results, sitagliptin is considered unlikely to cause interactions with other drugs that utilize these pathways.

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

Sitagliptin is not extensively bound to plasma proteins. Therefore, the propensity of sitagliptin to be involved in clinically meaningful drug-drug interactions mediated by plasma protein binding displacement is very low.

In Vivo Assessment of Drug Interactions

Effect of Sitagliptin on Other Drugs

In clinical studies, as described below, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glibenclamide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT). Multiple doses of sitagliptin slightly increased digoxin concentrations; however, these increases are not considered likely to be clinically meaningful and are not attributed to a specific mechanism.

Sulfonylureas: Single-dose pharmacokinetics of glibenclamide, a CYP2C9 substrate, were not meaningfully altered in subjects receiving multiple doses of sitagliptin. Clinically meaningful interactions would not be expected with other sulfonylureas (e.g., glipizide, tolbutamide, and glimepiride) which, like glibenclamide, are primarily eliminated by CYP2C9.

Simvastatin: Single-dose pharmacokinetics of simvastatin, a CYP3A4 substrate, were not meaningfully altered in subjects receiving multiple daily doses of sitagliptin. Therefore, sitagliptin is not an inhibitor of CYP3A4-mediated metabolism.

Thiazolidinediones: Single-dose pharmacokinetics of rosiglitazone were not meaningfully altered in subjects receiving multiple daily doses of sitagliptin. Therefore, sitagliptin is not an inhibitor of CYP2C8-mediated metabolism. Clinically meaningful interactions with pioglitazone are not expected because pioglitazone predominantly undergoes CYP2C8- or CYP3A4-mediated metabolism.

Warfarin: Multiple daily doses of sitagliptin did not meaningfully alter the pharmacokinetics, as assessed by measurement of S(-) or R(+) warfarin enantiomers, or pharmacodynamics (as assessed by measurement of prothrombin INR) of a single dose of warfarin. Since S(-) warfarin is primarily metabolized by CYP2C9, these data also support the conclusion that sitagliptin is not a CYP2C9 inhibitor.

Oral Contraceptives: Co-administration with sitagliptin did not meaningfully alter the steady-state pharmacokinetics of norethindrone or ethinyl estradiol.

Digoxin: Sitagliptin had a minimal effect on the pharmacokinetics of digoxin. Following administration of 0.25 mg digoxin concomitantly with 100 mg of sitagliptin daily for 10 days, the plasma AUC of digoxin was increased by 11%, and the plasma C_{max} by 18%. These increases are not considered to be clinically meaningful.

Effect of Other Drugs on Sitagliptin

Clinical data described below suggest that sitagliptin is not susceptible to clinically meaningful interactions by co-administered medications:

Cyclosporin: A study was conducted to assess the effect of cyclosporin, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Co-administration of a single 100-mg oral dose of JANUVIA® and a single 600-mg oral dose of cyclosporin increased the AUC and C_{max} of sitagliptin by approximately 29% and 68%, respectively. These modest changes in sitagliptin

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was also not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

Population Pharmacokinetics: 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, lansoprazole), and medications for erectile dysfunction (e.g., sildenafil).

Metformin hydrochloride

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

Frusemide: A single-dose, metformin-frusemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Frusemide 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 frusemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in frusemide renal clearance. No information is available about the interaction of metformin and frusemide when co-administered chronically.

Nifedipine: A single-dose, metformin-nifedipine drug 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 drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose metformin-cimetidine drug 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 drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other: Certain drugs tend to produce hyperglycaemia and may lead to loss of glycaemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs 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 drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

Effect on laboratory tests

Sitagliptin phosphate monohydrate

The incidence of laboratory adverse experiences was similar in patients treated with sitagliptin and metformin (7.6%) compared to patients treated with placebo and metformin (8.7%). In most but not all 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 **PRECAUTIONS**, *Metformin hydrochloride*).

ADVERSE REACTIONS

In placebo-controlled clinical trials, in patients with type 2 diabetes mellitus on metformin monotherapy, the addition of sitagliptin 100 mg daily was well tolerated. The overall incidence of adverse experiences reported in patients receiving sitagliptin and metformin was similar to that reported with patients receiving placebo and metformin.

In an additional, 104-week, placebo-controlled factorial study of initial therapy with sitagliptin in combination with metformin, the adverse reactions reported (regardless of investigator assessment of causality) in $\geq 5\%$ of patients are shown in Table 3.

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

Table 3
Initial Therapy with Combination of Sitagliptin and Metformin:
Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥5% of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Placebo)[†]

	Number of Patients (%)			
	Placebo/ Metformin 1000 mg bid	Sitagliptin (JANUVIA) 100 mg QD	Metformin 500 or 1000 mg bid ^{††}	Sitagliptin 50 mg bid + Metformin 500 or 1000 mg bid ^{††}
	N = 176	N = 179	N = 364 ^{††}	N = 372 ^{††}
Diarrhoea	12 (6.8)	8 (4.5)	37 (10.1)	44 (11.8)
Nausea	4 (2.3)	2 (1.1)	25 (6.9)	22 (5.9)
Bronchitis	8 (4.5)	3 (1.7)	14 (3.8)	27 (7.3)
Influenza	5 (2.8)	8 (4.5)	25 (6.9)	20 (5.4)
Upper Respiratory Tract Infection	13 (7.4)	12 (6.7)	37 (10.2)	45 (12.1)
Urinary Tract Infection	4 (2.3)	0 (0)	21 (5.8)	19 (5.1)
Arthralgia	3 (1.7)	7 (3.9)	18 (4.9)	20 (5.4)
Back Pain	9 (5.1)	9 (5.0)	16 (4.4)	24 (6.5)
Headache	7 (4.0)	6 (3.4)	21 (5.8)	27 (7.3)

[†] Intent-to-treat population.

^{††} Data pooled for the patients given the lower and higher doses of metformin.

Adverse reactions of hypoglycaemia were based on all reports of hypoglycaemia; a concurrent glucose measurement was not required. The overall incidence of pre-specified adverse reactions of hypoglycaemia in patients with type 2 diabetes mellitus inadequately controlled on diet and exercise was 2.8% in patients given placebo, 1.1% in patients given sitagliptin alone, 1.9% in patients given metformin alone and 3.8% in patients given sitagliptin in combination with metformin.

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

Treatment-emergent adverse events were reported in similar numbers across all treatment groups. Over the two-year treatment period, discontinuation due to loss of efficacy was reported more commonly in the 100 mg sitagliptin group than other treatment groups.

Sitagliptin as add-on Combination Therapy to Metformin

In a 24-week placebo-controlled trial of sitagliptin 100 mg administered once daily added to a twice daily metformin regimen (>1500 mg), there were no adverse experiences reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo. Discontinuation of therapy due to clinical adverse experiences was similar to the placebo treatment group (sitagliptin and metformin, 1.9%; placebo and metformin, 2.5%).

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. Adverse experiences of hypoglycaemia were based on all reports of hypoglycaemia; a concurrent glucose measurement was not required. 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.

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

Table 4 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 as Add-on to Metformin	
	Placebo and Metformin ≥ 1500 mg daily	Sitagliptin 100 mg and Metformin ≥ 1500 mg daily
	N= 237	N= 464
Hypoglycaemia	5 (2.1)	6 (1.3)
Diarrhoea	6 (2.5)	11 (2.4)
Nausea	2 (0.8)	6 (1.3)
Vomiting	2 (0.8)	5 (1.1)
Abdominal Pain	9 (3.8)	10 (2.2)

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 Experiences with Sitagliptin:

The most common adverse experience in sitagliptin monotherapy reported regardless of investigator assessment of causality in $\geq 5\%$ of patients and more commonly than in patients given placebo was nasopharyngitis.

Established Adverse Experiences with Metformin:

The most common ($>5\%$) established adverse experiences due to initiation of metformin therapy are diarrhoea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

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 antihyperglycaemic 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 drug exposure.

Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome (see **CONTRAINDICATIONS** and **PRECAUTIONS**, *Sitagliptin phosphate monohydrate*, Hypersensitivity Reactions); acute pancreatitis, including fatal and non-fatal haemorrhagic and necrotising pancreatitis (see **PRECAUTIONS**, *Pancreatitis*); worsening renal function, including acute renal failure (sometimes requiring dialysis); upper respiratory tract infection; nasopharyngitis; constipation; vomiting; headache; arthralgia; myalgia; pain in extremity; back pain.

DOSAGE AND ADMINISTRATION

Life-threatening lactic acidosis can occur due to accumulation of metformin. Risk factors include renal impairment, old age and the use of high doses of metformin above 2000 mg per day.

General

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

JANUMET should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to metformin. Patients should only be prescribed one strength of JANUMET at a time.

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

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/1000 mg metformin hydrochloride

As initial therapy:

For patients with type 2 diabetes mellitus, whose hyperglycaemia is inadequately controlled with diet and exercise alone, when dual therapy is appropriate, the recommended dose of JANUMET is 50 mg sitagliptin/500 mg metformin hydrochloride twice daily. Patients with inadequate glycaemic control on this dose should have their metformin dose increased up to a maximum of 50 mg sitagliptin/1000 mg metformin hydrochloride twice daily.

For patients inadequately controlled on sitagliptin monotherapy:

For patients inadequately controlled on sitagliptin alone, the recommended starting dose of JANUMET is 50 mg sitagliptin and 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 insufficiency should not be switched to JANUMET (see **CONTRAINDICATIONS**).

For patients inadequately controlled on metformin monotherapy

For patients not adequately 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 switching from sitagliptin co-administered with metformin

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

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 or ≥ 124 micromol/L [females], or abnormal creatinine clearance (< 60 mL/min) (see **CONTRAINDICATIONS**).

Elderly

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

OVERDOSAGE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

Sitagliptin phosphate monohydrate

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

Attachment 1: Product information for AusPAR Janumet Sitagliptin Merck Sharpe and Dohme (MSD) Australia Pty Ltd PM-2011-01226-3-5 Final 14 January 2013. This Product Information was approved at the time this AusPAR was published.

observed in one study at a dose of 800 mg sitagliptin (see **CLINICAL PHARMACOLOGY, 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 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 **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 drug from patients in whom metformin overdosage is suspected.

PRESENTATION AND STORAGE

JANUMET is available in the following presentations:

JANUMET Tablet 50 mg/500 mg - A light pink, film coated tablet with "575" on one side and plain on the other. Available in blister packs of 14(Starter Pack) and 56 tablets.

JANUMET Tablet 50 mg/850 mg - A pink, film coated tablet with "515" on one side and plain on the other. Available in blister packs of 14(Starter Pack) and 56 tablets.

JANUMET Tablet 50 mg/1000 mg - A red, film coated tablet with "577" on one side and plain on the other. Available in blister packs of 14(Starter Pack) and 56 tablets.

Store below 30°C. Store in original packaging.

NAME AND ADDRESS OF SPONSOR

MERCK SHARP & DOHME (AUSTRALIA) PTY LIMITED
54-68 FERDELL STREET
SOUTH GRANVILLE NSW 2142

POISON SCHEDULE

Prescription Only Medicine (Schedule 4)

This document was approved by the Therapeutic Goods Administration on 20th April 2009.
Date of most recent amendment 10 September 2012.