

DATA SHEET

1. PRODUCT NAME

JANUVIA[®] 25 mg film-coated tablets

JANUVIA[®] 50 mg film-coated tablets

JANUVIA[®] 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each JANUVIA 25 mg tablet contains sitagliptin phosphate monohydrate, equivalent to 25 mg sitagliptin.

Each JANUVIA 50 mg tablet contains sitagliptin phosphate monohydrate, equivalent to 50 mg sitagliptin.

Each JANUVIA 100 mg tablet contains sitagliptin phosphate monohydrate, equivalent to 100 mg sitagliptin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

25 mg tablet: A pink round film-coated tablet with 221 on one side and plain on the other.

50 mg tablet: A light beige round film-coated tablet with 112 on one side and plain on the other.

100 mg tablet: A beige round film-coated tablet with 277 on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Monotherapy

JANUVIA is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus.

Combination with metformin

JANUVIA is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin as initial therapy or when diet and exercise, plus the single agent do not provide adequate glycaemic control.

Combination with a sulfonylurea

JANUVIA is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with a sulfonylurea when treatment with the single agent alone, with diet and exercise, does not provide adequate glycaemic control.

Combination with a PPAR γ agonist

JANUVIA is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with a PPAR γ agonist (i.e. thiazolidinediones) as initial therapy or when the single agent alone, with diet and exercise, does not provide adequate glycaemic control.

Combination with metformin and a sulfonylurea

JANUVIA is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin and a sulfonylurea when dual therapy with these agents, with diet and exercise, does not provide adequate glycaemic control.

Combination with metformin and a PPAR γ agonist

JANUVIA is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin and a PPAR γ agonist (i.e. thiazolidinediones) when dual therapy with these agents, with diet and exercise, does not provide adequate glycaemic control.

Combination with insulin

JANUVIA 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 (with or without metformin).

4.2 Dose and method of administration

The recommended dose of JANUVIA is 100 mg once daily as monotherapy or as combination therapy with metformin, a sulfonylurea, insulin (with or without metformin), a PPAR γ agonist (i.e. thiazolidinediones), metformin plus a sulfonylurea, or metformin plus a PPAR γ agonist. JANUVIA can be taken with or without food.

When JANUVIA is used in combination with a sulfonylurea or with insulin, a lower dose of sulfonylurea or insulin may be considered to reduce the risk of sulfonylurea- or insulin-induced hypoglycaemia (See 4.4 Special warnings and precautions for use, *Hypoglycaemia in Combination with a Sulfonylurea or with Insulin*).

If a dose of JANUVIA is missed, it should be taken as soon as the patient remembers. A double dose of JANUVIA should not be taken on the same day.

Patients with renal impairment

Because there is a dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of JANUVIA and periodically thereafter. For patients with mild renal impairment (estimated glomerular filtration rate [eGFR] ≥ 60 mL/min/1.73 m² to < 90 mL/min/1.73 m²), no dosage adjustment for JANUVIA is required.

For patients with moderate renal impairment (eGFR ≥ 45 mL/min/1.73 m² to < 60 mL/min/1.73 m²), no dosage adjustment for JANUVIA is required.

For patients with moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m² to < 45 mL/min/1.73 m²), the dose of JANUVIA is 50 mg once daily.

For patients with severe renal impairment (eGFR ≥ 15 mL/min/1.73 m² to < 30 mL/min/1.73 m²) or with end-stage renal disease (ESRD) (eGFR < 15 mL/min/1.73 m²), including those requiring haemodialysis or peritoneal dialysis, the dose of JANUVIA is 25 mg once daily. JANUVIA may be administered without regard to the timing of dialysis.

Patients with hepatic impairment

No dosage adjustment is necessary for patients with mild to moderate hepatic impairment. JANUVIA has not been studied in patients with severe hepatic impairment.

Elderly

No dosage adjustment is necessary for elderly patients.

Paediatric population

There are no data available on the use of JANUVIA in patients younger than 18 years of age. Therefore, use of JANUVIA in paediatric patients is not recommended.

4.3 Contraindications

JANUVIA is contraindicated in patients who are hypersensitive to any components of this product (See 4.4 Special warnings and precautions for use, *Hypersensitivity Reactions* and Adverse effects, *Postmarketing Experience*).

4.4 Special warnings and precautions for use

General

JANUVIA 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, JANUVIA and other potentially suspect medicinal products should be discontinued.

Use in patients with renal impairment: JANUVIA is renally excreted. To achieve plasma concentrations of JANUVIA similar to those in patients with normal renal function, lower dosages are recommended in patients with $eGFR < 45 \text{ mL/min/1.73 m}^2$, as well as in ESRD patients requiring haemodialysis or peritoneal dialysis (See 4.2 Dose and method of administration, *Patients with renal impairment*).

Hypoglycaemia in combination with a sulfonylurea or with insulin: In clinical trials of JANUVIA 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 JANUVIA were similar to rates in patients taking placebo. As is typical with other anti-hyperglycaemic agents, when JANUVIA was used in combination with a sulfonylurea or with 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 JANUVIA. 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 JANUVIA, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUVIA, 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 JANUVIA. If bullous pemphigoid is suspected, JANUVIA should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Paediatric use

Safety and effectiveness of JANUVIA in paediatric patients under 18 years have not been established.

Use in the elderly

In clinical studies, the safety and effectiveness of JANUVIA in the elderly (≥ 65 years) were comparable to those seen in younger patients (< 65 years). No dosage adjustment is required based on age. Elderly patients are more likely to have renal impairment; as with other patients, dosage adjustment may be required in the presence of significant renal impairment (see 4.2 Dose and method of administration, *Patients with renal impairment*).

4.5 Interaction with other medicines and other forms of interaction

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.

Coadministration of multiple twice-daily doses of metformin with sitagliptin did not meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.

Population pharmacokinetic analyses have been conducted in patients with type 2 diabetes. Concomitant medications did not have a clinically meaningful effect on the pharmacokinetics of sitagliptin. 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), anti-hypertensives (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 likely to be clinically meaningful. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or JANUVIA is recommended.

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. No dosage adjustment for JANUVIA is recommended when coadministered with cyclosporine or other p-glycoprotein inhibitors (e.g. ketoconazole).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women; therefore, the safety of JANUVIA in pregnant women is not known. JANUVIA, like other oral anti-hyperglycaemic agents, is not recommended for use in pregnancy.

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.

Nursing mothers

Sitagliptin is secreted in the milk of lactating rats. It is not known whether sitagliptin is secreted in human milk. Therefore, JANUVIA 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 JANUVIA on the ability to drive and use machines have been performed. However, JANUVIA is not expected to affect the ability to drive and use machines.

4.8 Undesirable effects

JANUVIA was generally well tolerated in controlled clinical studies as both monotherapy and combination therapy, with discontinuation of therapy due to clinical adverse experiences similar to placebo.

In four placebo-controlled clinical studies as both monotherapy (one study of 18- and one of 24-week duration) and add-on combination therapy with metformin or pioglitazone (both of 24-week duration), there were 1082 patients treated with JANUVIA 100 mg once daily and 778 patients given placebo. (Two of these studies also included 456 patients treated with JANUVIA 200 mg daily, two times the recommended daily dose.) There were no medicine-related adverse reactions reported that occurred with an incidence of $\geq 1\%$ in patients receiving JANUVIA 100 mg. Overall, the safety profile of the 200-mg daily dose was similar to that of the 100-mg daily dose.

In a pre-specified pooled analysis of the above studies, the overall incidence of adverse experiences of hypoglycaemia in patients treated with JANUVIA 100 mg was similar to placebo (1.2% vs 0.9%). The incidences of selected gastrointestinal adverse experiences in patients treated with JANUVIA or placebo were: abdominal pain (JANUVIA, 2.3%; placebo, 2.1%), nausea (1.4%, 0.6%), vomiting (0.8%, 0.9%), and diarrhoea (3.0%, 2.3%).

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

Add-on combination with a sulfonylurea: In a 24-week placebo-controlled study of JANUVIA 100 mg in combination with glimepiride or with glimepiride and metformin (JANUVIA, N=222; placebo, N=219), the medicine-related adverse reaction reported in $\geq 1\%$ of patients treated with JANUVIA and more commonly than in patients treated with placebo was hypoglycaemia (JANUVIA, 9.5%; placebo, 0.9%).

Add-on combination with metformin and a PPAR γ agonist: In a placebo-controlled study of JANUVIA 100 mg in combination with metformin and rosiglitazone (JANUVIA, N=170; placebo, N=92), the medicine-related adverse reactions reported through the primary time point at Week 18 in $\geq 1\%$ of patients treated with JANUVIA and more commonly than in patients treated with placebo were: headache (JANUVIA, 2.4%; placebo, 0.0%), diarrhoea (1.8%, 1.1%), nausea (1.2%, 1.1%), hypoglycaemia (1.2%, 0.0%), and vomiting (1.2%, 0.0%). Through Week 54, the medicine-related adverse reactions reported in $\geq 1\%$ of patients treated with JANUVIA and more commonly than in patients treated with placebo were: headache (2.4%, 0.0%), hypoglycaemia (2.4%, 0.0%), upper respiratory tract infection (1.8%, 0.0%), nausea (1.2%, 1.1%), cough (1.2%, 0.0%), fungal skin infection (1.2%, 0.0%), peripheral oedema (1.2%, 0.0%), and vomiting (1.2%, 0.0%).

Initial combination therapy with metformin: In a 24-week placebo-controlled factorial study of initial therapy with sitagliptin 100 mg in combination with metformin at 1000 mg or 2000 mg per day (administered as sitagliptin 50 mg/metformin 500 mg or 1000 mg twice daily), the medicine-related adverse reactions reported in $\geq 1\%$ of patients treated with sitagliptin plus metformin (N=372) and more commonly than in patients treated with metformin alone (N=364) were: diarrhoea (sitagliptin plus metformin, 3.5%; metformin, 3.3%), dyspepsia (1.3%; 1.1%), flatulence (1.3%; 0.5%), vomiting (1.1%; 0.3%), and headache (1.3%; 1.1%). The incidence of hypoglycaemia was 1.1% in patients given sitagliptin in combination with metformin and 0.5% in patients given metformin alone.

Initial combination therapy with a PPAR γ agonist: In a 24-week study of initial therapy with JANUVIA at 100 mg/day in combination with pioglitazone at 30 mg/day, the only medicine-related adverse reaction reported in $\geq 1\%$ of patients treated with JANUVIA with pioglitazone (N=261) and more commonly than in patients treated with pioglitazone alone (N=259) was (asymptomatic) decreased blood glucose (JANUVIA with pioglitazone, 1.1%; pioglitazone, 0.0%). The incidence of (symptomatic) hypoglycaemia was 0.4% in patients given JANUVIA in combination with pioglitazone and 0.8% in patients given pioglitazone.

Add-on combination with insulin: In a 24 week placebo-controlled study of JANUVIA 100 mg in combination with insulin (with or without metformin), the drug-related adverse reactions reported in $\geq 1\%$ of patients treated with JANUVIA (N=322) and more commonly than in patients treated with placebo (N=319) were: hypoglycaemia (JANUVIA, 9.6%; placebo, 5.3%), influenza (1.2%, 0.3%), and headache (1.2%, 0.0%).

Pancreatitis: In a pooled analysis of 19 double-blind clinical trials that included data from 10,246 patients randomized 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*).

No clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed in patients treated with JANUVIA.

TECOS Cardiovascular safety study: The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7,332 patients treated with JANUVIA, 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 JANUVIA and 1,034 treated with placebo). The overall incidence of serious adverse events in patients receiving JANUVIA 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 JANUVIA-treated patients and 17.7% of the placebo-treated patients) and renal failure (1.4% of JANUVIA-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 JANUVIA-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 JANUVIA-treated patients and 0.7% in placebo-treated patients. The incidence of adjudication-confirmed pancreatitis events was 0.3% in JANUVIA-treated patients and 0.2% in placebo-treated patients. The incidence of adjudication-confirmed malignancy events was 3.7% in JANUVIA-treated patients and 4.0% in placebo-treated patients.

Postmarketing experience

Additional adverse reactions have been identified during postmarketing use of JANUVIA as monotherapy 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, *Hypersensitivity reactions*); acute pancreatitis, including fatal and non-fatal haemorrhagic and necrotising pancreatitis (see 4.4 Special warnings and precautions for use, *Pancreatitis*); worsening renal function, including acute renal failure (sometimes requiring dialysis); bullous pemphigoid (see 4.4 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

The incidence of laboratory adverse experiences was similar in patients treated with JANUVIA 100 mg compared to patients treated with placebo. 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 an 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.

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

During controlled clinical trials in healthy subjects, single doses of up to 800 mg JANUVIA 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 JANUVIA (see 5.1 Pharmacodynamic 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 JANUVIA 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Dipeptidyl peptidase 4 (DPP-4) inhibitors, ATC code: A10BH01.

JANUVIA (sitagliptin phosphate) is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. The DPP-4 inhibitors are

a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP). The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. This mechanism is unlike the mechanism seen with sulfonylureas; sulfonylureas cause insulin release even when glucose levels are low, which can lead to sulfonylurea-induced 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. Sitagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulfonylureas or meglitinides, biguanides, peroxisome proliferator-activated receptor gamma (PPAR γ) agonists, alpha-glucosidase inhibitors, and amylin analogues.

Mechanism of action

JANUVIA 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 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.

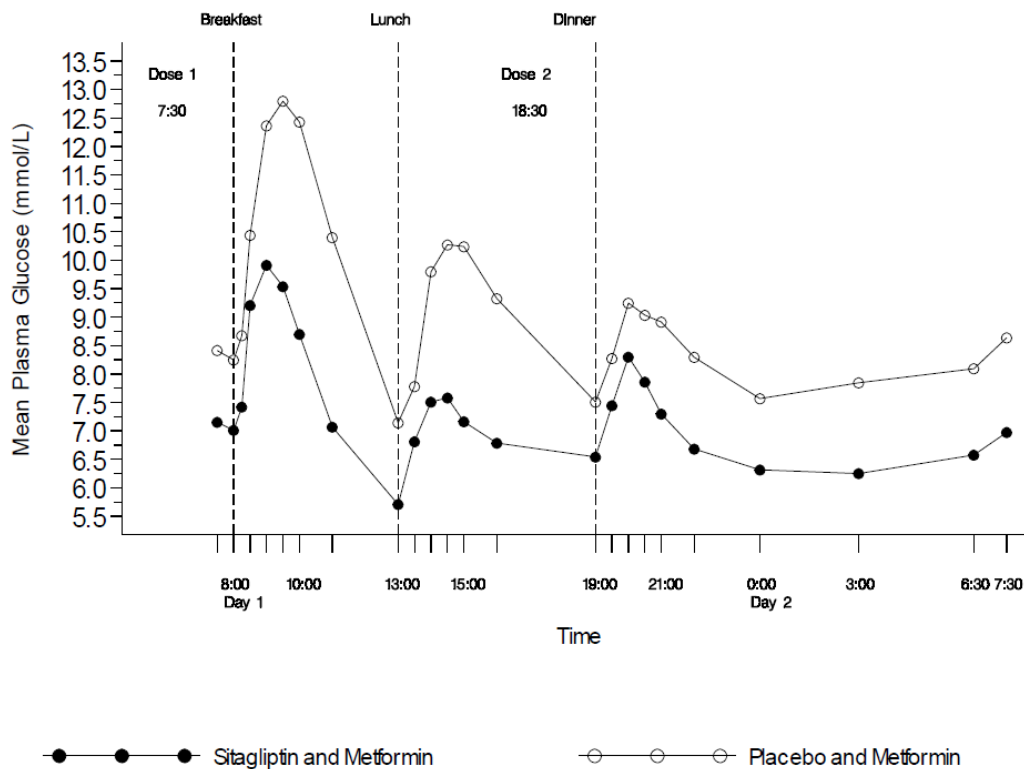
Further, GLP-1 does not impair the normal glucagon response to hypoglycaemia. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyses the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing 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. In patients with type 2 diabetes with hyperglycaemia, these changes in insulin and glucagon levels lead to lower haemoglobin A1c (HbA1c) and lower fasting and postprandial glucose concentrations. The glucose-dependent mechanism of sitagliptin is distinct from the mechanism of sulfonylureas, which increase 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.

General

In patients with type 2 diabetes, administration of single oral doses of JANUVIA 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 a study of patients with type 2 diabetes inadequately controlled on metformin monotherapy, glucose levels monitored throughout the day were significantly lower in patients who received sitagliptin 100 mg per day (50 mg twice daily) in combination with metformin compared with patients who received placebo with metformin (see Figure 1).

Figure 1 24-hour Plasma Glucose Profile after 4-Week Treatment with Sitagliptin 50 mg BID with Metformin or Placebo with Metformin



In Phase III clinical studies of 18- and 24-week duration, treatment with JANUVIA 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, JANUVIA 50 mg twice daily provided no additional glycaemic efficacy compared to 100 mg once daily.

In a randomised, placebo-controlled, double-blind, double-dummy, four-period crossover 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 by 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, JANUVIA 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 JANUVIA was generally well tolerated. In these patients, JANUVIA had a modest blood pressure lowering effect; 100 mg per day of JANUVIA 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 JANUVIA 100 mg, JANUVIA 800 mg (8 times the recommended dose), and placebo. At the recommended dose of 100 mg, there was no effect on the QTc interval obtained at the peak plasma concentration, or at any other time during the study. Following the 800-mg dose, the maximum increase in the placebo-corrected mean change in QTc from baseline at 3 hours post-dose was 8.0 msec. This small increase was not considered to be clinically significant. At the 800-mg dose, peak sitagliptin plasma concentrations were approximately 11 times higher than the peak concentrations following a 100-mg dose.

In patients with type 2 diabetes administered JANUVIA 100 mg (N=81) or JANUVIA 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

The pharmacokinetics of sitagliptin have been extensively characterised in healthy subjects and patients with type 2 diabetes. After oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose. Plasma AUC of sitagliptin increased in a dose-proportional manner. Following a single oral 100-mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 $\mu\text{M}\cdot\text{hr}$, C_{max} was 950 nM, and apparent terminal half-life ($t_{1/2}$) was 12.4 hours. Plasma AUC of sitagliptin increased approximately 14% following 100-mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of sitagliptin were generally similar in healthy subjects and in patients with type 2 diabetes.

Absorption

The absolute bioavailability of sitagliptin is approximately 87%. Since coadministration of a high-fat meal with JANUVIA had no effect on the pharmacokinetics, JANUVIA may be administered with or without food.

Distribution

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%).

Metabolism

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.

Elimination

Following administration of an oral [¹⁴C] 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.

Characteristics in patients

Gender

No dosage adjustment is necessary based on gender. 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.

Elderly

No dosage adjustment is required based on age. 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.

Race

No dosage adjustment is necessary based on race. 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.

Hepatic impairment

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 JANUVIA. These differences are not considered to be clinically meaningful. No dosage adjustment for JANUVIA is necessary for patients with mild or moderate hepatic impairment.

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.

Renal impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of JANUVIA (50 mg dose) in patients with varying degrees of chronic renal impairment compared to normal healthy control subjects. The study included patients with mild, moderate, and severe renal impairment, as well as patients with ESRD on haemodialysis. In addition, the effects of renal impairment on sitagliptin pharmacokinetics in patients with type 2 diabetes and mild, moderate or severe renal impairment (including ESRD) were assessed using population pharmacokinetic analyses.

Compared to normal healthy control subjects, plasma AUC of sitagliptin was increased by approximately 1.2-fold and 1.6-fold in patients with mild renal impairment (eGFR ≥ 60 mL/min/1.73 m² to < 90 mL/min/1.73 m²) and patients with moderate renal impairment (eGFR ≥ 45 mL/min/1.73 m² to < 60 mL/min/1.73 m²), respectively. Because increases of this magnitude are not clinically relevant, dosage adjustment in these patients is not necessary.

Plasma AUC of sitagliptin was increased approximately 2-fold in patients with moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m² to < 45 mL/min/1.73 m²), and approximately 4-fold in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²), including patients with ESRD on haemodialysis. Sitagliptin was modestly removed by haemodialysis (13.5% over a 3- to 4-hour haemodialysis session starting 4 hours post-dose). To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with eGFR < 45 mL/min/1.73 m². (See 4.2 Dose and method of administration, *Patients with renal impairment*).

Paediatric patients

No studies with JANUVIA have been performed in paediatric patients.

Body mass index (BMI)

No dosage adjustment is necessary based on BMI. Body mass index 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.

Type 2 diabetes

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

5.3 Preclinical safety data

Acute toxicity

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

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 administered sitagliptin 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.

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.

Carcinogenicity

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).

Mutagenesis

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.

Reproduction

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.

Development

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 JANUVIA contains the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate (calcium hydrogen phosphate, anhydrous), croscarmellose sodium, magnesium stearate, and sodium stearyl fumarate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol (macrogl), talc, titanium dioxide, red iron oxide, and yellow iron oxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C (86°F).

6.5 Nature and contents of container

Opaque blisters (PVC/PE/PVDC/aluminium). Packs of 7 tablets and 28 tablets.

Not all presentations may be available.

6.6 Special precautions for disposal

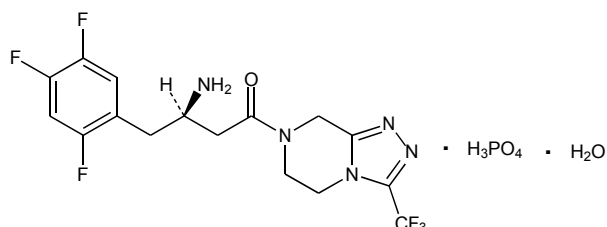
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Further information

Chemistry

JANUVIA tablets contain sitagliptin phosphate, an orally-active, potent, and selective inhibitor of dipeptidyl peptidase 4 (DPP-4), which is described chemically as: 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.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Merck Sharp & Dohme (New Zealand) Limited

P O Box 99851

Newmarket

Auckland

NEW ZEALAND

Tel: 0800 500 673

9. DATE OF FIRST APPROVAL

28 February 2008

10. DATE OF REVISION OF THE TEXT

5 April 2018

11. SUMMARY TABLE OF CHANGES

Date	Change
April 2018	4.2 Dose and method of administration, revised dosing recommendations for use in patients with renal impairment based on eGFR ranges. 4.4 Special warnings and precautions for use: revised precautionary text for use in patients with renal impairment based on eGFR ranges. 4.8 Undesirable effects, addition of 'Reporting of suspected adverse reactions' statement. 5.2 Pharmacokinetic properties- Characteristics in patients: revised text for renal impairment with a change from using creatinine clearance (CrCl) to estimated glomerular filtration rate (eGFR) to describe renal impairment.

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