SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

JANUVIA® 25 mg Tablets

JANUVIA® 50 mg Tablets

JANUVIA® 100 mg Tablets

COMPOSITION

Each film-coated JANUVIA Tablet contains 32,13; 64,25 or 128,5 mg of sitagliptin phosphate monohydrate, which is equivalent to 25, 50 or 100 mg, respectively, of free base.

JANUVIA Tablets are sugar free.

Inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate and sodium stearyl fumarate.

In addition, the film-coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol (macrogol), talc, titanium dioxide, red iron oxide and yellow iron oxide.

PHARMACOLOGICAL CLASSIFICATION

A.21.2 Oral Hypoglycaemics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Sitagliptin is an orally-active, potent and selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). Incretin hormones physiologically regulate blood glucose levels by increasing insulin response from pancreatic beta cells and suppressing glucagon secretion from pancreatic alpha cells, when blood glucose levels are normal or elevated. These effects are not observed when blood glucose levels are low.

Sitagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulphonylureas or meglitinides, biguanides, peroxisome proliferator-activated receptor gamma (PPARγ) agonists, alpha-glucosidase inhibitors and amylin analogues.

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 absorbed with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose. Plasma Area Under the Curve (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 micromolar hours, C_{max} was 950 nanomol 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 %. Co-administration of a high fat meal with sitagliptin has no effect on the pharmacokinetics (see **DOSAGE AND DIRECTIONS FOR USE**).

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

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may

be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, ciclosporin a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

Characteristics in Patients

Renal insufficiency: A single-dose, open-label study was conducted to evaluate the pharmacokinetics of sitagliptin (50 mg dose) in patients with varying degrees of chronic renal insufficiency compared to normal healthy control subjects. The study included patients with renal insufficiency, classified on the basis of creatinine clearance as mild (50 to < 80 ml/min), moderate (30 to < 50 ml/min) and severe (< 30 ml/min), as well as patients with end-stage renal disease on haemodialysis. Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula:

$$\text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)} \{\times 1{,}2\}}{[\text{serum creatinine } (\mu\text{mol/l})]}$$

For female patients: 0,85 x value calculated for males

Compared to normal healthy control subjects, an approximate 1,6-fold increase in plasma AUC of sitagliptin was observed in patients with mild renal insufficiency. An approximately 2,3-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal insufficiency, an approximately 3,8-fold increase was observed in patients with severe renal insufficiency and an approximately 4,5-fold increase was observed in patients with end-stage renal disease on haemodialysis, as compared to normal healthy control subjects. Sitagliptin was not meaningfully 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 moderate and severe renal insufficiency, as well as in end-stage renal disease patients requiring haemodialysis (see **DOSAGE AND DIRECTIONS FOR USE, Patients with renal insufficiency**).

Hepatic insufficiency: 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) (see **CONTRAINDICATIONS**).

Elderly: 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.

Paediatric: No studies with sitagliptin have been performed in paediatric patients.

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.

Body Mass Index (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.

Clinical Studies

Two placebo-controlled studies were conducted to evaluate the efficacy and safety of sitagliptin monotherapy. Treatment with sitagliptin at 100 mg provided significant improvements in HbA_{1c} (-0,60 % and -0,79 % change compared to placebo in the 18- and 24-week studies, respectively), fasting plasma glucose (FPG) and 2-hour post-prandial glucose (PPG), compared to placebo. Patients with a shorter length of time since diagnosis of diabetes (< 3 years) or with higher baseline HbA_{1c} had greater reductions in HbA_{1c}. In both studies, sitagliptin provided a significant reduction compared with placebo in FPG (-19,3 mg/dl in the 18-week study and -15,8 mg/dl in the 24-week study) at 3 weeks, the first time point at which FPG was measured.

In a study in patients with type 2 diabetes and chronic renal insufficiency (creatinine clearance < 30 ml/min and 30 to < 50 ml/min), the safety and tolerability of sitagliptin were generally similar to placebo.

Clinical studies were conducted to evaluate the efficacy and safety of sitagliptin in combination with metformin or a PPARγ agonist. In a placebo-controlled study of sitagliptin at 100 mg in combination with metformin, JANUVIA provided significant improvements in HbA_{1c}, (-0,65 % change compared to placebo), FPG and PPG. In a placebo-controlled study of sitagliptin in

combination with a PPARγ agonist, sitagliptin provided significant improvements in HbA_{1c} (-0,7 % change compared to placebo) and FPG.

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 Therapy

JANUVIA is also indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin or a PPARγ agonist (e.g. thiazolidinedione) when diet and exercise, plus the single agent do not provide adequate glycaemic control.

The combination of sitagliptin and sulphonylureas has not been adequately studied.

CONTRAINDICATIONS

JANUVIA is contraindicated in patients who are hypersensitive to any components of JANUVIA.

A history of serious hypersensitivity reactions, such as anaphylaxis and angioedema to JANUVIA or other gliptins (DPP-4).

JANUVIA has not been studied in patients with severe hepatic insufficiency (see **PHARMACOLOGICAL ACTION, Pharmacokinetic properties, Hepatic insufficiency**).

WARNINGS

Pancreatitis: In post-marketing experience there have been reports of acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotising pancreatitis (see **SIDE EFFECTS AND SPECIAL PRECAUTIONS, Side Effects, Post-marketing experience**), in patients taking JANUVIA. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent abdominal pain. Resolution of pancreatitis has been observed after discontinuation of JANUVIA. If pancreatitis is suspected, JANUVIA and other potentially suspect medicinal products should be discontinued immediately.

Hypersensitivity Reactions: There have been post-marketing reports of serious hypersensitivity reactions in patients treated with JANUVIA. These reactions include anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with JANUVIA, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUVIA immediately and institute an alternative class of medicines for treatment for diabetes (see CONTRAINDICATIONS and SIDE EFFECTS AND SPECIAL PRECAUTIONS, Side Effects, Post-marketing experience).

INTERACTIONS

In interaction studies, JANUVIA did not have clinically meaningful effects on the pharmacokinetics of the following: metformin, glyburide, simvastatin, warfarin and oral contraceptives. Based on these data, JANUVIA does not inhibit CYP isoenzymes CYP3A4, 2C8 or 2C9. Based on *in vitro* data, sitagliptin is also not expected to inhibit CYP2D6, 1A2, 2C19 or 2B6 or to induce CYP3A4. There is limited information on multiple dose co-administration of these agents.

There was a slight increase in the area under the curve (AUC 11 %) and mean peak medicine concentration (C_{max} 18 %) of digoxin with the co-administration of sitagliptin. These increases are not considered 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 JANUVIA were increased approximately 29 % and 68 % respectively, in subjects with co-administration of a single 100 mg oral dose of JANUVIA and a single 600 mg oral dose of ciclosporin, a potent probe inhibitor of p-glycoprotein. The observed changes in JANUVIA pharmacokinetics are not considered likely to be clinically meaningful. No dosage adjustment for JANUVIA is recommended when co-administered with ciclosporin or other p-glycoprotein inhibitors (e.g. ketoconazole).

A population pharmacokinetic analysis of patients and healthy subjects (n=858) on a wide variety of concomitant medications (n=83, approximately half of which are renally eliminated) indicated no clinically meaningful effects of these medicines on JANUVIA pharmacokinetics.

PREGNANCY AND LACTATION

Pregnancy

There are no studies in pregnant women; therefore, JANUVIA is not recommended for use in pregnancy.

Lactation

JANUVIA is secreted in the milk of lactating rats. It is not known whether JANUVIA is secreted in human milk. Therefore, JANUVIA should not be used by a woman who is breastfeeding.

DOSAGE AND DIRECTIONS FOR USE

JANUVIA can be taken with or without food.

The dose of JANUVIA in combination with metformin or a PPARγ agonist is 100 mg once daily. The dosage of metformin or PPARγ agonist should be maintained, and JANUVIA administered concomitantly.

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 insufficiency

For patients with mild renal insufficiency (creatinine clearance [CrCl] ≥ 50 ml/min, approximately corresponding to serum creatinine levels of ≤ 150 µmol/litre in men and ≤ 133 µmol/litre in women), no dosage adjustment for JANUVIA is required.

For patients with moderate renal insufficiency (CrCl ≥ 30 to < 50 ml/min, approximately corresponding to serum creatinine levels of > 150 µmol/litre to ≤ 265 µmol/litre in men and > 133 µmol/l to not ≤ 221 µmol/litre in women), the dose of JANUVIA is 50 mg once daily. This dose should be decreased if CrCl decreases to < 30ml/min.

For patients with severe renal insufficiency (CrCl < 30 ml/min, approximately corresponding to serum creatinine levels of > 265 µmol/litre in men and > 221 µmol/litre in women) or with end-stage renal disease requiring haemodialysis, the dose of JANUVIA is 25 mg once daily. JANUVIA may be administered without regard to the timing of haemodialysis.

Patients with hepatic insufficiency

No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency.

JANUVIA has not been studied in patients with severe hepatic insufficiency.

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.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side Effects

Adverse reactions considered as medicine related reported in patients treated with sitagliptin occurring in excess (> 0,2 % and difference more than one patient) of that in patients treated with placebo are listed below (**Table 1**) by system organ class and frequency. Frequencies are defined as: Very common (≥ 1/10), Common (≥ 1/100, < 1/10), Uncommon (≥ 1/1 000, < 1/100), Rare (≥ 1/10 000, < 1/1 000) and Very rare (< 1/10 000).

Table 1

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

Adverse Reaction	**Frequency of adverse reaction by treatment regimen**	
	Sitagliptin with Metformin	**Sitagliptin with a PPARγ Agent (pioglitazone)**
Investigations		
Decreased blood glucose levels	Uncommon	

Nervous system disorders		
Somnolence	Uncommon	
Gastrointestinal disorders		
Diarrhoea	Uncommon	
Nausea	Common	
Flatulence		Common
Upper abdominal pain	Uncommon	
Metabolism and nutrition disorders		
Hypoglycaemia		Common
General disorders		
Peripheral oedema		Common

In addition, in monotherapy studies of up to 24 weeks in duration of sitagliptin 100 mg once daily alone compared to placebo, adverse reactions considered as medicine-related reported in patients treated with sitagliptin in excess (> 0,2 % and difference more than 1 patient) of that in patients receiving placebo are headache, hypoglycaemia, constipation and dizziness.

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

Post-marketing experience

During post-marketing experience the following additional side effects have been reported: hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis and exfoliative skin conditions including Stevens-Johnson syndrome (see **SIDE EFFECTS AND SPECIAL PRECAUTIONS, Special Precautions**), acute pancreatitis, including fatal and non-fatal haemorrhagic and necrotising pancreatitis (see **WARNINGS, Pancreatitis**), worsening renal function, including acute renal failure (sometimes requiring dialysis); vomiting, headache, constipation, nasopharyngitis, upper respiratory tract infection.

Laboratory test findings

Across clinical studies, a small mean increase in uric acid (approximately 12 µmol/litre difference from placebo; mean baseline 297 to 327 µmol/litre) was found in patients treated with JANUVIA 100 or 200 mg daily. No increase in the incidence of gout was reported. A small mean decrease in total alkaline phosphatase (up to approximately 5 IU/l difference from placebo; mean baseline approximately 56 to 62 IU/l) was also observed, partly related to a small decrease in bone alkaline phosphatase. A small increase in white blood cell count (WBC) (approximately 200 cells/µlitre difference in WBC versus placebo; mean baseline WBC approximately 6 600 cells/µlitre) was observed due to an increase in neutrophils. This observation was seen in most but not all studies. These changes in laboratory parameters are not considered to be clinically relevant.

Special Precautions

General

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

Hypoglycaemia: The use of JANUVIA in combination with medications known to cause hypoglycaemia, such as sulphonylureas or insulin, has not been adequately studied.

Renal insufficiency: A dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with end-stage renal disease requiring haemodialysis (see **DOSAGE AND DIRECTIONS FOR USE, Patients with renal insufficiency**).

Effects on Ability to Drive and Use Machinery

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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. There is no experience with doses above 800 mg in humans.

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.

JANUVIA 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 JANUVIA is dialysable by peritoneal dialysis.

IDENTIFICATION

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

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

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

PRESENTATION

JANUVIA 25 mg, 50 mg and 100 mg is packed in opaque PVDC/PE/PVC push-through blisters (referred to as PVDC blister) with push-through aluminium lidding. Packs contain 28 tablets with blisters of 14 tablets. The blisters are opened by pushing the tablets through the foil.

STORAGE INSTRUCTIONS

Store at or below 30 °C. Protect from moisture.

Keep out of reach of children.

The blister should be kept in the carton until required for use.

REGISTRATION NUMBERS

JANUVIA 25 mg: 41/21.2/0354

JANUVIA 50 mg: 41/21.2/0355

JANUVIA 100 mg: 41/21.2/0356

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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DATE OF PUBLICATION OF THE PACKAGE INSERT

14 September 2012

WPC-JAN-T-122005 (partial 04-2010)