欧州添付文書

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Januvia 25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Round, pink film-coated tablet with "221" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For patients with type 2 diabetes mellitus, Januvia is indicated:

- to improve glycaemic control when diet and exercise alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
- to improve glycaemic control in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- to improve glycaemic control in combination with a sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
- to improve glycaemic control in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.

For patients with type 2 diabetes mellitus in whom use of a PPARγ agonist (i.e. a thiazolidinedione) is appropriate, Januvia is indicated:

- in combination with the PPARγ agonist when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control.
- in combination with the PPARγ agonist and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.

4.2 Posology and method of administration

The dose of Januvia is 100 mg once daily. When sitagliptin is used in combination with metformin and/or a PPARγ agonist, the dosage of metformin and/or PPARγ agonist should be maintained, and sitagliptin administered concomitantly.

When Januvia is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. (See section 4.4.)

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

Januvia can be taken with or without food.

Patients with renal insufficiency
For patients with mild renal insufficiency (creatinine clearance [CrCl] ≥ 50 ml/min), no dosage adjustment for Januvia is required.

Clinical study experience with Januvia in patients with moderate or severe renal insufficiency is limited. Therefore, use of Januvia is not recommended in this patient population (see section 5.2).

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 based on age. Limited safety data is available in patients ≥ 75 years of age and care should be exercised.

Paediatric population
Januvia is not recommended for use in children below 18 years of age due to a lack of data on its safety and efficacy.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 4.4 and 4.8).

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.

Hypoglycaemia when used in combination with other anti-hyperglycaemic agents
In clinical trials of Januvia as monotherapy and as part of combination therapy with agents not known to cause hypoglycaemia (i.e. metformin and/or a PPARγ agonist), rates of hypoglycaemia reported with sitagliptin were similar to rates in patients taking placebo. When sitagliptin was added to a sulphonylurea, the incidence of hypoglycaemia was increased over that of placebo (see section 4.8). Therefore, to reduce the risk of hypoglycaemia, a lower dose of sulphonylurea may be considered (see section 4.2). The use of sitagliptin in combination with insulin has not been adequately studied.

Renal insufficiency
As the experience is limited, patients with moderate to severe renal insufficiency should not be treated with Januvia (see section 5.2).

Hypersensitivity Reactions
Postmarketing reports of serious hypersensitivity reactions in patients treated with Januvia have been reported. 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, assess for other potential causes for the event, and institute alternative treatment for diabetes. (See section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on sitagliptin
Clinical data described below suggest that the risk for clinically meaningful interactions by co-administered medicinal products is low.

Metformin: Co-administration of multiple twice-daily doses of 1000 mg metformin with 50 mg sitagliptin did not meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.

Cyclosporine: A study was conducted to assess the effect of cyclosporine, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Coadministration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of cyclosporine increased the AUC and C_{max} of sitagliptin by approximately 29 % and 68 %, respectively. These changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin is CYP3A4, with contribution from CYP2C8. In patients with normal renal function, metabolism, including via CYP3A4, plays only a small role in the clearance of sitagliptin. Metabolism may play a more significant role in the elimination of sitagliptin in the setting of severe renal insufficiency or ESRD. For this reason, it is possible that potent CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the phamacokinetics of sitagliptin in patients with severe renal insufficiency or ESRD. The effects of potent CYP3A4 inhibitors in the setting of renal insufficiency has not been assessed in a clinical study.

In vitro transport studies showed that sitagliptin is a substrate for p-glycoprotein and OAT3. OAT3 mediated transport of sitagliptin was inhibited *in vitro* by probenecid, although the risk of clinically meaningful interactions is considered to be low. Concomitant administration of OAT3 inhibitors has not been evaluated *in vivo*.

Effects of sitagliptin on other medicinal products
In vitro data suggest that sitagliptin does not inhibit nor induce CYP450 isoenzymes. In clinical studies, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing *in vivo* evidence of a low propensity for causing interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT).

Sitagliptin had a small effect on plasma digoxin concentrations, and may be a mild inhibitor of p-glycoprotein *in vivo*.

Digoxin: Sitagliptin had a small effect on plasma digoxin concentrations. Following administration of 0.25 mg digoxin concomitantly with 100 mg of Januvia daily for 10 days, the plasma AUC of digoxin was increased on average by 11 %, and the plasma C_{max} on average by 18 %. No dosage adjustment of digoxin is recommended. However, patients at risk of digoxin toxicity should be monitored for this when sitagliptin and digoxin are administered concomitantly.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of Januvia in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). The potential risk for humans is unknown. Due to lack of human data, Januvia should not be used during pregnancy.

Lactation
It is unknown whether sitagliptin is excreted in human breast milk. Animal studies have shown excretion of sitagliptin in breast milk. Januvia should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving or operating machines, it should be taken into account that dizziness and somnolence have been reported.

4.8 Undesirable effects

In 10 large clinical trials of up to 2 years in duration, over 2900 patients have received treatment with Januvia 100 mg per day alone or in combination with metformin, a sulphonylurea (with or without metformin) or a PPARγ agent (with or without metformin). In a pooled analysis of 9 of these trials, the rate of discontinuation due to adverse experiences considered drug-related was 0.8 % with 100 mg per day and 1.5 % with other treatments. No adverse reactions considered as drug-related were reported in patients treated with sitagliptin occurring in excess (> 0.2 % and difference > 1 patient) of that in patients treated with control. In an additional combination study with a PPARγ agent (rosiglitazone) and metformin, no patients were discontinued due to adverse experiences considered as drug-related.

Adverse reactions considered as drug-related reported in patients treated with sitagliptin occurring in excess (> 0.2 % and difference > 1 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 (≥ 1/1000, < 1/100); rare (≥ 1/10000, < 1/1000); and very rare (< 1/10000).

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[1]	**Sitagliptin with a Sulfonylurea[2]**	**Sitagliptin with a Sulfonylurea and Metformin[3]**	**Sitagliptin with a PPARγ Agent (pioglitazone)[4]**	**Sitagliptin with a PPARγ Agent (rosiglitazone) and Metformin[5]**
Time-point	**24-week**	**24-week**	**24-week**	**24-week**	**18-week**
Investigations					
blood glucose decreased	Uncommon				
Nervous system disorders					
headache					Common
somnolence	Uncommon				
Gastrointestinal disorders					
diarrhoea	Uncommon				Common
nausea	Common				
flatulence				Common	
constipation			Common		
upper abdominal pain	Uncommon				

vomiting					Common
Metabolism and nutrition disorders					
hypoglycaemia*		Very common	Very common	Common	Common
General disorders					
peripheral oedema				Common	Common†

* In clinical trials of Januvia as monotherapy and sitagliptin as part of combination therapy with metformin and/or a PPARγ agent, rates of hypoglycaemia reported with sitagliptin were similar to rates in patients taking placebo.

† Observed in the 54-week analysis.

[1] In this placebo-controlled 24-week study of sitagliptin 100 mg once daily in combination with metformin, the incidence of adverse reactions considered as drug-related in patients treated with sitagliptin/metformin compared to treatment with placebo/metformin was 9.3 % and 10.1 %, respectively.

In an additional 1-year study of sitagliptin 100 mg once daily in combination with metformin, the incidence of adverse reactions considered as drug-related in patients treated with sitagliptin/metformin compared to sulphonylurea/metformin was 14.5 % and 30.3 %, respectively.

In pooled studies of up to 1 year in duration comparing sitagliptin/metformin to a sulphonylurea agent/metformin, adverse reactions considered as drug-related reported in patients treated with sitagliptin 100 mg occurring in excess (> 0.2 % and difference > 1 patient) of that in patients receiving the sulphonylurea agent are as follows: anorexia (Metabolism and nutritional disorders; frequency uncommon) and weight decreased (Investigations; frequency uncommon).

[2] In this 24-week study of sitagliptin 100 mg once daily in combination with glimepiride, the incidence of adverse reactions considered as drug-related in patients treated with sitagliptin/glimepiride compared to treatment with placebo/glimepiride was 11.3 % and 6.6 %, respectively.

[3] In this 24-week study of sitagliptin 100 mg once daily in combination with glimepiride and metformin, the incidence of adverse reactions considered as drug-related in patients treated with sitagliptin in combination with glimepiride/metformin compared to treatment with placebo in combination with glimepiride/metformin was 18.1 % and 7.1 %, respectively.

[4] In this 24-week study of the combination of sitagliptin 100 mg once daily and pioglitazone, the incidence of adverse reactions considered as drug-related in patients treated with sitagliptin/pioglitazone compared to patients treated with placebo/pioglitazone was 9.1 % and 9.0 %, respectively.

[5] In this study of sitagliptin 100 mg once daily in combination with rosiglitazone and metformin, which continued through 54 weeks, the incidence of adverse reactions considered as drug-related in patients treated with the sitagliptin combination compared to treatment with the placebo combination was 15.3 % and 10.9 %, respectively. Other drug-related adverse reactions reported in the 54-week analysis (frequency common) in patients treated with the sitagliptin combination occurring in excess (> 0.2 % and difference > 1 patient) of that in patients treated with the placebo combination were: headache, cough, vomiting, hypoglycaemia, fungal skin infection, and upper respiratory tract infection.

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 drug-related reported in patients treated with sitagliptin in excess (> 0.2 % and difference > 1 patient) of that in patients receiving placebo are headache, hypoglycaemia, constipation, and dizziness.

In addition to the drug-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 > 0.5 % higher with Januvia than that in the control group) included osteoarthritis and pain in extremity.

In an additional 24-week study of sitagliptin 100 mg once daily compared to metformin, the incidence of adverse reactions considered as drug-related in patients treated with sitagliptin compared to metformin was 5.9 % and 16.7 %, respectively, primarily due to a higher incidence of gastrointestinal adverse reactions in the metformin group. In this study 0.6 % of patients treated with sitagliptin and 2.3 % of patients treated with metformin were discontinued due to adverse experiences considered as drug-related.

In a 24-week study of initial combination therapy with sitagliptin and metformin administered twice daily (sitagliptin/metformin 50 mg/500 mg or 50 mg/1000 mg), the overall incidence of adverse reactions considered as drug-related in patients treated with the combination of sitagliptin and metformin compared to patients treated with placebo was 14.0 % and 9.7 %, respectively. The overall incidence of adverse reactions considered as drug-related in patients treated with the combination of sitagliptin and metformin was comparable to metformin alone (14.0 % each) and greater than sitagliptin alone (6.7 %), with the differences relative to sitagliptin alone primarily due to gastrointestinal adverse reactions.

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.

No clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed with Januvia treatment.

Post-marketing Experience:
During post-marketing experience the following additional side effects have been reported (frequency not known): hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, and exfoliative skin conditions including Stevens-Johnson syndrome (see section 4.4).

4.9 Overdose

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were generally well tolerated. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. 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 dialyzable. In clinical studies, approximately 13.5 % of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: DPP-4 Inhibitor, ATC code: A10BH01.

Januvia is a member of a class of oral anti-hyperglycaemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors. The improvement in glycaemic control observed with this agent may be mediated by enhancing the levels of active incretin hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling 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 hydrolyzes 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 hemoglobin A_{1c} (HbA_{1c}) and lower fasting and postprandial glucose concentrations. The glucose-dependent mechanism of sitagliptin is distinct from the mechanism of sulphonylureas, 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.

In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Co-administration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations.

Overall, sitagliptin improved glycaemic control when given as monotherapy, when used in combination with metformin (initial or add-on therapy), in combination with a sulphonylurea (with or without metformin), in combination with a thiazolidinedione, and in combination with a thiazolidinedione and metformin, as measured by clinically relevant reductions in HbA_{1c} from baseline at study endpoint (see Table 2).

Two studies were conducted to evaluate the efficacy and safety of Januvia monotherapy. Treatment with sitagliptin at 100 mg once daily as monotherapy provided significant improvements in HbA_{1c}, fasting plasma glucose (FPG), and 2-hour post-prandial glucose (2-hour PPG), compared to placebo in two studies, one of 18- and one of 24-weeks duration. Improvement of surrogate markers of beta cell function, including HOMA-β (Homeostasis Model Assessment-β), proinsulin to insulin ratio, and

measures of beta cell responsiveness from the frequently-sampled meal tolerance test were observed. The observed incidence of hypoglycaemia in patients treated with Januvia was similar to placebo. Body weight did not increase from baseline with sitagliptin therapy in either study, compared to a small reduction in patients given placebo.

In a study in patients with type 2 diabetes and chronic renal insufficiency (creatinine clearance < 50 ml/min), the safety and tolerability of reduced doses of sitagliptin were investigated and generally similar to placebo. In addition, the reductions in HbA_{1c} and FPG with sitagliptin compared to placebo were generally similar to those observed in other monotherapy studies in patients with normal renal function (see section 5.2). The number of patients with moderate to severe renal insufficiency was too low to confirm safe use of sitagliptin in this type of patients.

Sitagliptin 100 mg once daily provided significant improvements in glycaemic parameters compared with placebo in two 24-week studies of sitagliptin as add-on therapy, one in combination with metformin and one in combination with pioglitazone. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo. In these studies there was a similar incidence of hypoglycaemia reported for patients treated with sitagliptin or placebo.

A 24-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to glimepiride alone or glimepiride in combination with metformin. The addition of sitagliptin to either glimepiride alone or to glimepiride and metformin provided significant improvements in glycaemic parameters. Patients treated with sitagliptin had a modest increase in body weight compared to those given placebo.

A 54-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to the combination of rosiglitazone and metformin. The addition of sitagliptin to rosiglitazone and metformin provided significant improvements in glycaemic parameters at the primary timepoint of Week 18, with improvements sustained through the end of the study. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo (1.9 vs. 1.3 kg).

In a 24-week placebo-controlled factorial study of initial therapy, sitagliptin 50 mg twice daily in combination with metformin (500 mg or 1000 mg twice daily) provided significant improvements in glycaemic parameters compared with either monotherapy. The decrease in body weight with the combination of sitagliptin and metformin was similar to that observed with metformin alone or placebo; there was no change from baseline for patients on sitagliptin alone. The incidence of hypoglycaemia was similar across treatment groups.

Table 2. HbA_{1c} results in placebo-controlled monotherapy and combination therapy studies*

Study	Mean baseline HbA_{1c} (%)	Mean change from baseline HbA_{1c} (%)†	Placebo-corrected mean change in HbA_{1c} (%)† (95 % CI)
Monotherapy Studies			
Sitagliptin 100 mg once daily§ (N= 193)	8.0	-0.5	-0.6‡ (-0.8, -0.4)
Sitagliptin 100 mg once daily‖ (N= 229)	8.0	-0.6	-0.8‡ (-1.0, -0.6)
Combination Therapy Studies			
Sitagliptin 100 mg once daily added to ongoing metformin therapy‖ (N=453)	8.0	-0.7	-0.7‡ (-0.8, -0.5)
Sitagliptin 100 mg once daily added to ongoing pioglitazone therapy‖ (N=163)	8.1	-0.9	-0.7‡ (-0.9, -0.5)
Sitagliptin 100 mg once daily added to ongoing glimepiride therapy‖ (N=102)	8.4	-0.3	-0.6‡ (-0.8, -0.3)
Sitagliptin 100 mg once daily added to ongoing glimepiride + metformin therapy‖ (N=115)	8.3	-0.6	-0.9‡ (-1.1, -0.7)
Sitagliptin 100 mg once daily added to ongoing rosiglitazone + metformin therapy (N=170)			
Week 18	8.8	-1.0	-0.7‡ (-0.9, -0.5)
Week 54	8.8	-1.0	-0.8‡ (-1.0, -0.5)
Initial therapy (twice daily)‖: Sitagliptin 50 mg + metformin 500 mg (N=183)	8.8	-1.4	-1.6‡ (-1.8, -1.3)
Initial therapy (twice daily)‖: Sitagliptin 50 mg + metformin 1000 mg (N=178)	8.8	-1.9	-2.1‡ (-2.3, -1.8)

* 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 or placebo + combination treatment.

§ HbA_{1c} (%) at week 18.

‖ HbA_{1c} (%) at week 24.

A 24-week active (metformin)-controlled study was designed to evaluate the efficacy and safety of sitagliptin 100 mg once daily (N=528) compared to metformin (N=522) in patients with inadequate glycaemic control on diet and exercise and who were not on anti-hyperglycaemic therapy (off therapy for at least 4 months). The mean dose of metformin was approximately 1900 mg per day. The reduction in HbA_{1c} from mean baseline values of 7.2 % was -0.38 % for sitagliptin and -0.55 % for metformin. The overall incidence of gastrointestinal adverse reactions considered as drug-related in patients treated with sitagliptin was 2.7 % compared with 12.6 % in patients treated with metformin. The incidence of hypoglycaemia was not significantly different between the treatment groups

(sitagliptin, 1.3 %; metformin, 1.9 %). Body weight decreased from baseline in both groups (sitagliptin, -0.6 kg; metformin -1.9 kg).

In a study comparing the efficacy and safety of the addition of Januvia 100 mg once daily or glipizide (a sulphonylurea agent) in patients with inadequate glycaemic control on metformin monotherapy, sitagliptin was similar to glipizide in reducing HbA_{1c}. The mean glipizide dose used in the comparator group was 10 mg per day with approximately 40 % of patients requiring a glipizide dose of ≤ 5 mg/day throughout the study. However, more patients in the sitagliptin group discontinued due to lack of efficacy than in the glipizide group. 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 vs. +1.1 kg). 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 %).

5.2 Pharmacokinetic properties

Absorption
Following 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, mean plasma AUC of sitagliptin was 8.52 μM•hr, C_{max} was 950 nM. 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.

Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for C_{max} and C_{24hr} (C_{max} increased in a greater than dose-proportional manner and C_{24hr} increased in a less than dose-proportional manner).

Distribution
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 %).

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.

In vitro data showed that sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4 and CYP1A2.

Elimination
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. Sitagliptin accumulates only minimally with multiple doses. The 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. Sitagliptin is not a substrate for OCT2 or OAT1 or PEPT1/2 transporters. *In vitro*, sitagliptin did not inhibit OAT3 (IC50=160 μM) or p-glycoprotein (up to 250 μM) mediated transport at therapeutically relevant plasma concentrations. In a clinical study sitagliptin had a small effect on plasma digoxin concentrations indicating that sitagliptin may be a mild inhibitor of p-glycoprotein.

Characteristics in patients
The pharmacokinetics of sitagliptin were generally similar in healthy subjects and in patients with type 2 diabetes.

Renal insufficiency
A single-dose, open-label study was conducted to evaluate the pharmacokinetics of a reduced dose of sitagliptin (50-mg) 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 (ESRD) on hemodialysis.

Patients with mild renal insufficiency did not have a clinically meaningful increase in the plasma concentration of sitagliptin as compared to normal healthy control subjects. 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 hemodialysis, as compared to normal healthy control subjects. Sitagliptin was modestly removed by hemodialysis (13.5 % over a 3- to 4-hour hemodialysis session starting 4 hours postdose). Januvia is not recommended for use in patients with moderate or severe renal insufficiency including those with ESRD since experience in these patients is too limited. (See section 4.2.)

Hepatic insufficiency
No dosage adjustment for Januvia is necessary for patients with mild or moderate hepatic insufficiency (Child-Pugh score ≤ 9). 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.

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.

Paediatric
No studies with Januvia have been performed in paediatric patients.

Other patient characteristics
No dosage adjustment is necessary based on gender, race, or body mass index (BMI). These characteristics had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

5.3 Preclinical safety data

Renal and liver toxicity were observed in rodents at systemic exposure values 58 times the human exposure level, while the no-effect level was found at 19 times the human exposure level. Incisor teeth abnormalities were observed in rats at exposure levels 67 times the clinical exposure level; the no-effect level for this finding was 58-fold based on the 14-week rat study. The relevance of these findings for humans is unknown. Transient treatment-related physical signs, some of which suggest neural toxicity, such as open-mouth breathing, salivation, white foamy emesis, ataxia, trembling, decreased activity, and/or hunched posture were observed in dogs at exposure levels approximately

23 times the clinical exposure level. In addition, very slight to slight skeletal muscle degeneration was also observed histologically at doses resulting in systemic exposure levels of approximately 23 times the human exposure level. A no-effect level for these findings was found at an exposure 6-fold the clinical exposure level.

Sitagliptin has not been demonstrated to be genotoxic in preclinical studies. Sitagliptin was not carcinogenic in mice. In rats, there was an increased incidence of hepatic adenomas and carcinomas at systemic exposure levels 58 times the human exposure level. Since hepatotoxicity has been shown to correlate with induction of hepatic neoplasia in rats, this increased incidence of hepatic tumors in rats was likely secondary to chronic hepatic toxicity at this high dose. Because of the high safety margin (19-fold at this no-effect level), these neoplastic changes are not considered relevant for the situation in humans.

No adverse effects upon fertility were observed in male and female rats given sitagliptin prior to and throughout mating.

In a pre-/postnatal development study performed in rats sitagliptin showed no adverse effects.

Reproductive toxicity studies showed a slight treatment-related increased incidence of fetal rib malformations (absent, hypoplastic and wavy ribs) in the offspring of rats at systemic exposure levels more than 29 times the human exposure levels. Maternal toxicity was seen in rabbits at more than 29 times the human exposure levels. Because of the high safety margins, these findings do not suggest a relevant risk for human reproduction. Sitagliptin is secreted in considerable amounts into the milk of lactating rats (milk/plasma ratio: 4:1).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
microcrystalline cellulose (E460)
calcium hydrogen phosphate, anhydrous (E341)
croscarmellose sodium (E468)
magnesium stearate (E470b)
sodium stearyl fumarate

Film coating:
polyvinyl alcohol
macrogol 3350
talc (E553b)
titanium dioxide (E171)
red iron oxide (E172)
yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Opaque blisters (PVC/PE/PVDC and aluminum). Packs of 14, 28, 56, 84 or 98 film-coated tablets and 50 x 1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd.
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/383/001
EU/1/07/383/002
EU/1/07/383/003
EU/1/07/383/004
EU/1/07/383/005
EU/1/07/383/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 March 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Januvia 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Round, light beige film-coated tablet with "112" on one side.

4. CLINICAL PARTICULARS

For patients with type 2 diabetes mellitus, Januvia is indicated:

- to improve glycaemic control when diet and exercise alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
- to improve glycaemic control in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- to improve glycaemic control in combination with a sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
- to improve glycaemic control in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.

For patients with type 2 diabetes mellitus in whom use of a PPARγ agonist (i.e. a thiazolidinedione) is appropriate, Januvia is indicated:

- in combination with the PPARγ agonist when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control.
- in combination with the PPARγ agonist and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.

4.2 Posology and method of administration

The dose of Januvia is 100 mg once daily. When sitagliptin is used in combination with metformin and/or a PPARγ agonist, the dosage of metformin and/or PPARγ agonist should be maintained, and sitagliptin administered concomitantly.

When Januvia is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. (See section 4.4.)

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

Januvia can be taken with or without food.

Patients with renal insufficiency
For patients with mild renal insufficiency (creatinine clearance [CrCl] ≥ 50 ml/min), no dosage adjustment for Januvia is required.

Clinical study experience with Januvia in patients with moderate or severe renal insufficiency is limited. Therefore, use of Januvia is not recommended in this patient population (see section 5.2).

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 based on age. Limited safety data is available in patients ≥ 75 years of age and care should be exercised.

Paediatric population
Januvia is not recommended for use in children below 18 years of age due to a lack of data on its safety and efficacy.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 4.4 and 4.8).

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.

Hypoglycaemia when used in combination with other anti-hyperglycaemic agents
In clinical trials of Januvia as monotherapy and as part of combination therapy with agents not known to cause hypoglycaemia (i.e. metformin and/or a PPARγ agonist), rates of hypoglycaemia reported with sitagliptin were similar to rates in patients taking placebo. When sitagliptin was added to a sulphonylurea, the incidence of hypoglycaemia was increased over that of placebo (see section 4.8). Therefore, to reduce the risk of hypoglycaemia, a lower dose of sulphonylurea may be considered (see section 4.2). The use of sitagliptin in combination with insulin has not been adequately studied.

Renal insufficiency
As the experience is limited, patients with moderate to severe renal insufficiency should not be treated with Januvia (see section 5.2).

Hypersensitivity Reactions
Postmarketing reports of serious hypersensitivity reactions in patients treated with Januvia have been reported. 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, assess for other potential causes for the event, and institute alternative treatment for diabetes. (See section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on sitagliptin
Clinical data described below suggest that the risk for clinically meaningful interactions by co-administered medicinal products is low.

Metformin: Co-administration of multiple twice-daily doses of 1000 mg metformin with 50 mg sitagliptin did not meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.

Cyclosporine: A study was conducted to assess the effect of cyclosporine, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Coadministration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of cyclosporine increased the AUC and C_{max} of sitagliptin by approximately 29 % and 68 %, respectively. These changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin is CYP3A4, with contribution from CYP2C8. In patients with normal renal function, metabolism, including via CYP3A4, plays only a small role in the clearance of sitagliptin. Metabolism may play a more significant role in the elimination of sitagliptin in the setting of severe renal insufficiency or ESRD. For this reason, it is possible that potent CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the phamacokinetics of sitagliptin in patients with severe renal insufficiency or ESRD. The effects of potent CYP3A4 inhibitors in the setting of renal insufficiency has not been assessed in a clinical study.

In vitro transport studies showed that sitagliptin is a substrate for p-glycoprotein and OAT3. OAT3 mediated transport of sitagliptin was inhibited *in vitro* by probenecid, although the risk of clinically meaningful interactions is considered to be low. Concomitant administration of OAT3 inhibitors has not been evaluated *in vivo*.

Effects of sitagliptin on other medicinal products
In vitro data suggest that sitagliptin does not inhibit nor induce CYP450 isoenzymes. In clinical studies, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing *in vivo* evidence of a low propensity for causing interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT).

Sitagliptin had a small effect on plasma digoxin concentrations, and may be a mild inhibitor of p-glycoprotein *in vivo*.

Digoxin: Sitagliptin had a small effect on plasma digoxin concentrations. Following administration of 0.25 mg digoxin concomitantly with 100 mg of Januvia daily for 10 days, the plasma AUC of digoxin was increased on average by 11 %, and the plasma C_{max} on average by 18 %. No dosage adjustment of digoxin is recommended. However, patients at risk of digoxin toxicity should be monitored for this when sitagliptin and digoxin are administered concomitantly.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of Januvia in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). The potential risk for humans is unknown. Due to lack of human data, Januvia should not be used during pregnancy.

Lactation
It is unknown whether sitagliptin is excreted in human breast milk. Animal studies have shown excretion of sitagliptin in breast milk. Januvia should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving or operating machines, it should be taken into account that dizziness and somnolence have been reported.

4.8 Undesirable effects

In 10 large clinical trials of up to 2 years in duration, over 2900 patients have received treatment with Januvia 100 mg per day alone or in combination with metformin, a sulphonylurea (with or without metformin) or a PPARγ agent (with or without metformin). In a pooled analysis of 9 of these trials, the rate of discontinuation due to adverse experiences considered drug-related was 0.8 % with 100 mg per day and 1.5 % with other treatments. No adverse reactions considered as drug-related were reported in patients treated with sitagliptin occurring in excess (> 0.2 % and difference > 1 patient) of that in patients treated with control. In an additional combination study with a PPARγ agent (rosiglitazone) and metformin, no patients were discontinued due to adverse experiences considered as drug-related.

Adverse reactions considered as drug-related reported in patients treated with sitagliptin occurring in excess (> 0.2 % and difference > 1 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 (≥ 1/1000, < 1/100); rare (≥ 1/10000, < 1/1000); and very rare (< 1/10000).

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[1]	**Sitagliptin with a Sulfonylurea[2]**	**Sitagliptin with a Sulfonylurea and Metformin[3]**	**Sitagliptin with a PPARγ Agent (pioglitazone)[4]**	**Sitagliptin with a PPARγ Agent (rosiglitazone) and Metformin[5]**
Time-point	**24-week**	**24-week**	**24-week**	**24-week**	**18-week**
Investigations					
blood glucose decreased	Uncommon				
Nervous system disorders					
headache					Common
somnolence	Uncommon				
Gastrointestinal disorders					
diarrhoea	Uncommon				Common
nausea	Common				
flatulence				Common	
constipation			Common		
upper abdominal pain	Uncommon				
vomiting					Common
Metabolism and nutrition					

disorders					
hypoglycaemia*		Very common	Very common	Common	Common
General disorders					
peripheral oedema				Common	Common†

* In clinical trials of Januvia as monotherapy and sitagliptin as part of combination therapy with metformin and/or a PPARγ agent, rates of hypoglycaemia reported with sitagliptin were similar to rates in patients taking placebo.

† Observed in the 54-week analysis.

[1] In this placebo-controlled 24-week study of sitagliptin 100 mg once daily in combination with metformin, the incidence of adverse reactions considered as drug-related in patients treated with sitagliptin/metformin compared to treatment with placebo/metformin was 9.3 % and 10.1 %, respectively.

In an additional 1-year study of sitagliptin 100 mg once daily in combination with metformin, the incidence of adverse reactions considered as drug-related in patients treated with sitagliptin/metformin compared to sulphonylurea/metformin was 14.5 % and 30.3 %, respectively.

In pooled studies of up to 1 year in duration comparing sitagliptin/metformin to a sulphonylurea agent/metformin, adverse reactions considered as drug-related reported in patients treated with sitagliptin 100 mg occurring in excess (> 0.2 % and difference > 1 patient) of that in patients receiving the sulphonylurea agent are as follows: anorexia (Metabolism and nutritional disorders; frequency uncommon) and weight decreased (Investigations; frequency uncommon).

[2] In this 24-week study of sitagliptin 100 mg once daily in combination with glimepiride, the incidence of adverse reactions considered as drug-related in patients treated with sitagliptin/glimepiride compared to treatment with placebo/glimepiride was 11.3 % and 6.6 %, respectively.

[3] In this 24-week study of sitagliptin 100 mg once daily in combination with glimepiride and metformin, the incidence of adverse reactions considered as drug-related in patients treated with sitagliptin in combination with glimepiride/metformin compared to treatment with placebo in combination with glimepiride/metformin was 18.1 % and 7.1 %, respectively.

[4] In this 24-week study of the combination of sitagliptin 100 mg once daily and pioglitazone, the incidence of adverse reactions considered as drug-related in patients treated with sitagliptin/pioglitazone compared to patients treated with placebo/pioglitazone was 9.1 % and 9.0 %, respectively.

[5] In this study of sitagliptin 100 mg once daily in combination with rosiglitazone and metformin, which continued through 54 weeks, the incidence of adverse reactions considered as drug-related in patients treated with the sitagliptin combination compared to treatment with the placebo combination was 15.3 % and 10.9 %, respectively. Other drug-related adverse reactions reported in the 54-week analysis (frequency common) in patients treated with the sitagliptin combination occurring in excess (> 0.2 % and difference > 1 patient) of that in patients treated with the placebo combination were: headache, cough, vomiting, hypoglycaemia, fungal skin infection, and upper respiratory tract infection.

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 drug-related reported in patients treated with sitagliptin in excess (> 0.2 % and difference > 1 patient) of that in patients receiving placebo are headache, hypoglycaemia, constipation, and dizziness.

In addition to the drug-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 > 0.5 % higher with Januvia than that in the control group) included osteoarthritis and pain in extremity.

In an additional 24-week study of sitagliptin 100 mg once daily compared to metformin, the incidence of adverse reactions considered as drug-related in patients treated with sitagliptin compared to metformin was 5.9 % and 16.7 %, respectively, primarily due to a higher incidence of gastrointestinal adverse reactions in the metformin group. In this study 0.6 % of patients treated with sitagliptin and 2.3 % of patients treated with metformin were discontinued due to adverse experiences considered as drug-related.

In a 24-week study of initial combination therapy with sitagliptin and metformin administered twice daily (sitagliptin/metformin 50 mg/500 mg or 50 mg/1000 mg), the overall incidence of adverse reactions considered as drug-related in patients treated with the combination of sitagliptin and metformin compared to patients treated with placebo was 14.0 % and 9.7 %, respectively. The overall incidence of adverse reactions considered as drug-related in patients treated with the combination of sitagliptin and metformin was comparable to metformin alone (14.0 % each) and greater than sitagliptin alone (6.7 %), with the differences relative to sitagliptin alone primarily due to gastrointestinal adverse reactions.

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.

No clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed with Januvia treatment.

Post-marketing Experience:
During post-marketing experience the following additional side effects have been reported (frequency not known): hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, and exfoliative skin conditions including Stevens-Johnson syndrome (see section 4.4).

4.9 Overdose

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were generally well tolerated. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. 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 dialyzable. In clinical studies, approximately 13.5 % of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: DPP-4 Inhibitor, ATC code: A10BH01.

Januvia is a member of a class of oral anti-hyperglycaemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors. The improvement in glycaemic control observed with this agent may be mediated by enhancing the levels of active incretin hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling 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 hydrolyzes 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 hemoglobin A_{1c} (HbA_{1c}) and lower fasting and postprandial glucose concentrations. The glucose-dependent mechanism of sitagliptin is distinct from the mechanism of sulphonylureas, 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.

In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Co-administration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations.

Overall, sitagliptin improved glycaemic control when given as monotherapy, when used in combination with metformin (initial or add-on therapy), in combination with a sulphonylurea (with or without metformin), in combination with a thiazolidinedione, and in combination with a thiazolidinedione and metformin, as measured by clinically relevant reductions in HbA_{1c} from baseline at study endpoint (see Table 2).

Two studies were conducted to evaluate the efficacy and safety of Januvia monotherapy. Treatment with sitagliptin at 100 mg once daily as monotherapy provided significant improvements in HbA_{1c}, fasting plasma glucose (FPG), and 2-hour post-prandial glucose (2-hour PPG), compared to placebo in two studies, one of 18- and one of 24-weeks duration. Improvement of surrogate markers of beta cell function, including HOMA-β (Homeostasis Model Assessment-β), proinsulin to insulin ratio, and measures of beta cell responsiveness from the frequently-sampled meal tolerance test were observed. The observed incidence of hypoglycaemia in patients treated with Januvia was similar to placebo. Body weight did not increase from baseline with sitagliptin therapy in either study, compared to a small reduction in patients given placebo.

In a study in patients with type 2 diabetes and chronic renal insufficiency (creatinine clearance < 50 ml/min), the safety and tolerability of reduced doses of sitagliptin were investigated and generally similar to placebo. In addition, the reductions in HbA_{1c} and FPG with sitagliptin compared to placebo were generally similar to those observed in other monotherapy studies in patients with normal renal function (see section 5.2). The number of patients with moderate to severe renal insufficiency was too low to confirm safe use of sitagliptin in this type of patients.

Sitagliptin 100 mg once daily provided significant improvements in glycaemic parameters compared with placebo in two 24-week studies of sitagliptin as add-on therapy, one in combination with metformin and one in combination with pioglitazone. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo. In these studies there was a similar incidence of hypoglycaemia reported for patients treated with sitagliptin or placebo.

A 24-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to glimepiride alone or glimepiride in combination with metformin. The addition of sitagliptin to either glimepiride alone or to glimepiride and metformin provided significant improvements in glycaemic parameters. Patients treated with sitagliptin had a modest increase in body weight compared to those given placebo.

A 54-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to the combination of rosiglitazone and metformin. The addition of sitagliptin to rosiglitazone and metformin provided significant improvements in glycaemic parameters at the primary timepoint of Week 18, with improvements sustained through the end of the study. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo (1.9 vs. 1.3 kg).

In a 24-week placebo-controlled factorial study of initial therapy, sitagliptin 50 mg twice daily in combination with metformin (500 mg or 1000 mg twice daily) provided significant improvements in glycaemic parameters compared with either monotherapy. The decrease in body weight with the combination of sitagliptin and metformin was similar to that observed with metformin alone or placebo; there was no change from baseline for patients on sitagliptin alone. The incidence of hypoglycaemia was similar across treatment groups.

Table 2. HbA_{1c} results in placebo-controlled monotherapy and combination therapy studies*

Study	Mean baseline HbA_{1c} (%)	Mean change from baseline HbA_{1c} (%)†	Placebo-corrected mean change in HbA_{1c} (%)† (95 % CI)
Monotherapy Studies			
Sitagliptin 100 mg once daily§ (N= 193)	8.0	-0.5	-0.6‡ (-0.8, -0.4)
Sitagliptin 100 mg once daily‖ (N= 229)	8.0	-0.6	-0.8‡ (-1.0, -0.6)
Combination Therapy Studies			
Sitagliptin 100 mg once daily added to ongoing metformin therapy‖ (N=453)	8.0	-0.7	-0.7‡ (-0.8, -0.5)
Sitagliptin 100 mg once daily added to ongoing pioglitazone therapy‖ (N=163)	8.1	-0.9	-0.7‡ (-0.9, -0.5)
Sitagliptin 100 mg once daily added to ongoing glimepiride therapy‖ (N=102)	8.4	-0.3	-0.6‡ (-0.8, -0.3)
Sitagliptin 100 mg once daily added to ongoing glimepiride + metformin therapy‖ (N=115)	8.3	-0.6	-0.9‡ (-1.1, -0.7)
Sitagliptin 100 mg once daily added to ongoing rosiglitazone + metformin therapy (N=170)			
Week 18	8.8	-1.0	-0.7‡ (-0.9, -0.5)
Week 54	8.8	-1.0	-0.8‡ (-1.0, -0.5)
Initial therapy (twice daily)‖: Sitagliptin 50 mg + metformin 500 mg (N=183)	8.8	-1.4	-1.6‡ (-1.8, -1.3)
Initial therapy (twice daily)‖: Sitagliptin 50 mg + metformin 1000 mg (N=178)	8.8	-1.9	-2.1‡ (-2.3, -1.8)

* 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 or placebo + combination treatment.

§ HbA_{1c} (%) at week 18.

‖ HbA_{1c} (%) at week 24.

A 24-week active (metformin)-controlled study was designed to evaluate the efficacy and safety of sitagliptin 100 mg once daily (N=528) compared to metformin (N=522) in patients with inadequate glycaemic control on diet and exercise and who were not on anti-hyperglycaemic therapy (off therapy for at least 4 months). The mean dose of metformin was approximately 1900 mg per day. The reduction in HbA_{1c} from mean baseline values of 7.2 % was -0.38 % for sitagliptin and -0.55 % for metformin. The overall incidence of gastrointestinal adverse reactions considered as drug-related in patients treated with sitagliptin was 2.7 % compared with 12.6 % in patients treated with metformin. The incidence of hypoglycaemia was not significantly different between the treatment groups

(sitagliptin, 1.3 %; metformin, 1.9 %). Body weight decreased from baseline in both groups (sitagliptin, -0.6 kg; metformin -1.9 kg).

In a study comparing the efficacy and safety of the addition of Januvia 100 mg once daily or glipizide (a sulphonylurea agent) in patients with inadequate glycaemic control on metformin monotherapy, sitagliptin was similar to glipizide in reducing HbA_{1c}. The mean glipizide dose used in the comparator group was 10 mg per day with approximately 40 % of patients requiring a glipizide dose of ≤ 5 mg/day throughout the study. However, more patients in the sitagliptin group discontinued due to lack of efficacy than in the glipizide group. 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 vs. +1.1 kg). 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 %).

5.2 Pharmacokinetic properties

Absorption
Following 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, mean plasma AUC of sitagliptin was 8.52 μM•hr, C_{max} was 950 nM. 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.

Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for C_{max} and C_{24hr} (C_{max} increased in a greater than dose-proportional manner and C_{24hr} increased in a less than dose-proportional manner).

Distribution
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 %).

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.

In vitro data showed that sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4 and CYP1A2.

Elimination
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. Sitagliptin accumulates only minimally with multiple doses. The 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. Sitagliptin is not a substrate for OCT2 or OAT1 or PEPT1/2 transporters. *In vitro*, sitagliptin did not inhibit OAT3 (IC50=160 μM) or p-glycoprotein (up to 250 μM) mediated transport at therapeutically relevant plasma concentrations. In a clinical study sitagliptin had a small effect on plasma digoxin concentrations indicating that sitagliptin may be a mild inhibitor of p-glycoprotein.

Characteristics in patients
The pharmacokinetics of sitagliptin were generally similar in healthy subjects and in patients with type 2 diabetes.

Renal insufficiency
A single-dose, open-label study was conducted to evaluate the pharmacokinetics of a reduced dose of sitagliptin (50-mg) 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 (ESRD) on hemodialysis.

Patients with mild renal insufficiency did not have a clinically meaningful increase in the plasma concentration of sitagliptin as compared to normal healthy control subjects. 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 hemodialysis, as compared to normal healthy control subjects. Sitagliptin was modestly removed by hemodialysis (13.5 % over a 3- to 4-hour hemodialysis session starting 4 hours postdose). Januvia is not recommended for use in patients with moderate or severe renal insufficiency including those with ESRD since experience in these patients is too limited. (See section 4.2.)

Hepatic insufficiency
No dosage adjustment for Januvia is necessary for patients with mild or moderate hepatic insufficiency (Child-Pugh score ≤ 9). 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.

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.

Paediatric
No studies with Januvia have been performed in paediatric patients.

Other patient characteristics
No dosage adjustment is necessary based on gender, race, or body mass index (BMI). These characteristics had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

5.3 Preclinical safety data

Renal and liver toxicity were observed in rodents at systemic exposure values 58 times the human exposure level, while the no-effect level was found at 19 times the human exposure level. Incisor teeth abnormalities were observed in rats at exposure levels 67 times the clinical exposure level; the no-effect level for this finding was 58-fold based on the 14-week rat study. The relevance of these findings for humans is unknown. Transient treatment-related physical signs, some of which suggest neural toxicity, such as open-mouth breathing, salivation, white foamy emesis, ataxia, trembling, decreased activity, and/or hunched posture were observed in dogs at exposure levels approximately

23 times the clinical exposure level. In addition, very slight to slight skeletal muscle degeneration was also observed histologically at doses resulting in systemic exposure levels of approximately 23 times the human exposure level. A no-effect level for these findings was found at an exposure 6-fold the clinical exposure level.

Sitagliptin has not been demonstrated to be genotoxic in preclinical studies. Sitagliptin was not carcinogenic in mice. In rats, there was an increased incidence of hepatic adenomas and carcinomas at systemic exposure levels 58 times the human exposure level. Since hepatotoxicity has been shown to correlate with induction of hepatic neoplasia in rats, this increased incidence of hepatic tumors in rats was likely secondary to chronic hepatic toxicity at this high dose. Because of the high safety margin (19-fold at this no-effect level), these neoplastic changes are not considered relevant for the situation in humans.

No adverse effects upon fertility were observed in male and female rats given sitagliptin prior to and throughout mating.

In a pre-/postnatal development study performed in rats sitagliptin showed no adverse effects.

Reproductive toxicity studies showed a slight treatment-related increased incidence of fetal rib malformations (absent, hypoplastic and wavy ribs) in the offspring of rats at systemic exposure levels more than 29 times the human exposure levels. Maternal toxicity was seen in rabbits at more than 29 times the human exposure levels. Because of the high safety margins, these findings do not suggest a relevant risk for human reproduction. Sitagliptin is secreted in considerable amounts into the milk of lactating rats (milk/plasma ratio: 4:1).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
microcrystalline cellulose (E460)
calcium hydrogen phosphate, anhydrous (E341)
croscarmellose sodium (E468)
magnesium stearate (E470b)
sodium stearyl fumarate

Film coating:
polyvinyl alcohol
macrogol 3350
talc (E553b)
titanium dioxide (E171)
red iron oxide (E172)
yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Opaque blisters (PVC/PE/PVDC and aluminum). Packs of 14, 28, 56, 84 or 98 film-coated tablets and 50 x 1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd.
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/383/007
EU/1/07/383/008
EU/1/07/383/009
EU/1/07/383/010
EU/1/07/383/011
EU/1/07/383/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 March 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Januvia 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Round, beige film-coated tablet with "277" on one side.

4. CLINICAL PARTICULARS

For patients with type 2 diabetes mellitus, Januvia is indicated:

- to improve glycaemic control when diet and exercise alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
- to improve glycaemic control in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- to improve glycaemic control in combination with a sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
- to improve glycaemic control in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.

For patients with type 2 diabetes mellitus in whom use of a PPARγ agonist (i.e. a thiazolidinedione) is appropriate, Januvia is indicated:

- in combination with the PPARγ agonist when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control.
- in combination with the PPARγ agonist and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.

4.2 Posology and method of administration

The dose of Januvia is 100 mg once daily. When sitagliptin is used in combination with metformin and/or a PPARγ agonist, the dosage of metformin and/or PPARγ agonist should be maintained, and sitagliptin administered concomitantly.

When Januvia is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia. (See section 4.4.)

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

Januvia can be taken with or without food.

Patients with renal insufficiency
For patients with mild renal insufficiency (creatinine clearance [CrCl] ≥50 ml/min), no dosage adjustment for Januvia is required.

Clinical study experience with Januvia in patients with moderate or severe renal insufficiency is limited. Therefore, use of Januvia is not recommended in this patient population (see section 5.2).

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 based on age. Limited safety data is available in patients ≥ 75 years of age and care should be exercised.

Paediatric population
Januvia is not recommended for use in children below 18 years of age due to a lack of data on its safety and efficacy.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 4.4 and 4.8).

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.

Hypoglycaemia when used in combination with other anti-hyperglycaemic agents
In clinical trials of Januvia as monotherapy and as part of combination therapy with agents not known to cause hypoglycaemia (i.e. metformin and/or a PPARγ agonist), rates of hypoglycaemia reported with sitagliptin were similar to rates in patients taking placebo. When sitagliptin was added to a sulphonylurea, the incidence of hypoglycaemia was increased over that of placebo (see section 4.8). Therefore, to reduce the risk of hypoglycaemia, a lower dose of sulphonylurea may be considered (see section 4.2). The use of sitagliptin in combination with insulin has not been adequately studied.

Renal insufficiency
As the experience is limited, patients with moderate to severe renal insufficiency should not be treated with Januvia (see section 5.2).

Hypersensitivity Reactions
Postmarketing reports of serious hypersensitivity reactions in patients treated with Januvia have been reported. 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, assess for other potential causes for the event, and institute alternative treatment for diabetes. (See section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on sitagliptin
Clinical data described below suggest that the risk for clinically meaningful interactions by co-administered medicinal products is low.

Metformin: Co-administration of multiple twice-daily doses of 1000 mg metformin with 50 mg sitagliptin did not meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.

Cyclosporine: A study was conducted to assess the effect of cyclosporine, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Coadministration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of cyclosporine increased the AUC and C_{max} of sitagliptin by approximately 29 % and 68 %, respectively. These changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin is CYP3A4, with contribution from CYP2C8. In patients with normal renal function, metabolism, including via CYP3A4, plays only a small role in the clearance of sitagliptin. Metabolism may play a more significant role in the elimination of sitagliptin in the setting of severe renal insufficiency or ESRD. For this reason, it is possible that potent CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the phamacokinetics of sitagliptin in patients with severe renal insufficiency or ESRD. The effects of potent CYP3A4 inhibitors in the setting of renal insufficiency has not been assessed in a clinical study.

In vitro transport studies showed that sitagliptin is a substrate for p-glycoprotein and OAT3. OAT3 mediated transport of sitagliptin was inhibited *in vitro* by probenecid, although the risk of clinically meaningful interactions is considered to be low. Concomitant administration of OAT3 inhibitors has not been evaluated *in vivo*.

Effects of sitagliptin on other medicinal products
In vitro data suggest that sitagliptin does not inhibit nor induce CYP450 isoenzymes. In clinical studies, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing *in vivo* evidence of a low propensity for causing interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT).

Sitagliptin had a small effect on plasma digoxin concentrations, and may be a mild inhibitor of p-glycoprotein *in vivo*.

Digoxin: Sitagliptin had a small effect on plasma digoxin concentrations. Following administration of 0.25 mg digoxin concomitantly with 100 mg of Januvia daily for 10 days, the plasma AUC of digoxin was increased on average by 11 %, and the plasma C_{max} on average by 18 %. No dosage adjustment of digoxin is recommended. However, patients at risk of digoxin toxicity should be monitored for this when sitagliptin and digoxin are administered concomitantly.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of Januvia in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). The potential risk for humans is unknown. Due to lack of human data, Januvia should not be used during pregnancy.

Lactation
It is unknown whether sitagliptin is excreted in human breast milk. Animal studies have shown excretion of sitagliptin in breast milk. Januvia should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving or operating machines, it should be taken into account that dizziness and somnolence have been reported.

4.8 Undesirable effects

In 10 large clinical trials of up to 2 years in duration, over 2900 patients have received treatment with Januvia 100 mg per day alone or in combination with metformin, a sulphonylurea (with or without metformin) or a PPARγ agent (with or without metformin). In a pooled analysis of 9 of these trials, the rate of discontinuation due to adverse experiences considered drug-related was 0.8 % with 100 mg per day and 1.5 % with other treatments. No adverse reactions considered as drug-related were reported in patients treated with sitagliptin occurring in excess (> 0.2 % and difference > 1 patient) of that in patients treated with control. In an additional combination study with a PPARγ agent (rosiglitazone) and metformin, no patients were discontinued due to adverse experiences considered as drug-related.

Adverse reactions considered as drug-related reported in patients treated with sitagliptin occurring in excess (> 0.2 % and difference > 1 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 (≥ 1/1000, < 1/100); rare (≥ 1/10000, < 1/1000); and very rare (< 1/10000).

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[1]	**Sitagliptin with a Sulfonylurea[2]**	**Sitagliptin with a Sulfonylurea and Metformin[3]**	**Sitagliptin with a PPARγ Agent (pioglitazone)[4]**	**Sitagliptin with a PPARγ Agent (rosiglitazone) and Metformin[5]**
Time-point	**24-week**	**24-week**	**24-week**	**24-week**	**18-week**
Investigations					
blood glucose decreased	Uncommon				
Nervous system disorders					
headache					Common
somnolence	Uncommon				
Gastrointestinal disorders					
diarrhoea	Uncommon				Common
nausea	Common				
flatulence				Common	
constipation			Common		
upper abdominal pain	Uncommon				
vomiting					Common
Metabolism and nutrition					

disorders					
hypoglycaemia*		Very common	Very common	Common	Common
General disorders					
peripheral oedema				Common	Common†

* In clinical trials of Januvia as monotherapy and sitagliptin as part of combination therapy with metformin and/or a PPARγ agent, rates of hypoglycaemia reported with sitagliptin were similar to rates in patients taking placebo.

† Observed in the 54-week analysis.

[1] In this placebo-controlled 24-week study of sitagliptin 100 mg once daily in combination with metformin, the incidence of adverse reactions considered as drug-related in patients treated with sitagliptin/metformin compared to treatment with placebo/metformin was 9.3 % and 10.1 %, respectively.

In an additional 1-year study of sitagliptin 100 mg once daily in combination with metformin, the incidence of adverse reactions considered as drug-related in patients treated with sitagliptin/metformin compared to sulphonylurea/metformin was 14.5 % and 30.3 %, respectively.

In pooled studies of up to 1 year in duration comparing sitagliptin/metformin to a sulphonylurea agent/metformin, adverse reactions considered as drug-related reported in patients treated with sitagliptin 100 mg occurring in excess (> 0.2 % and difference > 1 patient) of that in patients receiving the sulphonylurea agent are as follows: anorexia (Metabolism and nutritional disorders; frequency uncommon) and weight decreased (Investigations; frequency uncommon).

[2] In this 24-week study of sitagliptin 100 mg once daily in combination with glimepiride, the incidence of adverse reactions considered as drug-related in patients treated with sitagliptin/glimepiride compared to treatment with placebo/glimepiride was 11.3 % and 6.6 %, respectively.

[3] In this 24-week study of sitagliptin 100 mg once daily in combination with glimepiride and metformin, the incidence of adverse reactions considered as drug-related in patients treated with sitagliptin in combination with glimepiride/metformin compared to treatment with placebo in combination with glimepiride/metformin was 18.1 % and 7.1 %, respectively.

[4] In this 24-week study of the combination of sitagliptin 100 mg once daily and pioglitazone, the incidence of adverse reactions considered as drug-related in patients treated with sitagliptin/pioglitazone compared to patients treated with placebo/pioglitazone was 9.1 % and 9.0 %, respectively.

[5] In this study of sitagliptin 100 mg once daily in combination with rosiglitazone and metformin, which continued through 54 weeks, the incidence of adverse reactions considered as drug-related in patients treated with the sitagliptin combination compared to treatment with the placebo combination was 15.3 % and 10.9 %, respectively. Other drug-related adverse reactions reported in the 54-week analysis (frequency common) in patients treated with the sitagliptin combination occurring in excess (> 0.2 % and difference > 1 patient) of that in patients treated with the placebo combination were: headache, cough, vomiting, hypoglycaemia, fungal skin infection, and upper respiratory tract infection.

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 drug-related reported in patients treated with sitagliptin in excess (> 0.2 % and difference > 1 patient) of that in patients receiving placebo are headache, hypoglycaemia, constipation, and dizziness.

In addition to the drug-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 > 0.5 % higher with Januvia than that in the control group) included osteoarthritis and pain in extremity.

In an additional 24-week study of sitagliptin 100 mg once daily compared to metformin, the incidence of adverse reactions considered as drug-related in patients treated with sitagliptin compared to metformin was 5.9 % and 16.7 %, respectively, primarily due to a higher incidence of gastrointestinal adverse reactions in the metformin group. In this study 0.6 % of patients treated with sitagliptin and 2.3 % of patients treated with metformin were discontinued due to adverse experiences considered as drug-related.

In a 24-week study of initial combination therapy with sitagliptin and metformin administered twice daily (sitagliptin/metformin 50 mg/500 mg or 50 mg/1000 mg), the overall incidence of adverse reactions considered as drug-related in patients treated with the combination of sitagliptin and metformin compared to patients treated with placebo was 14.0 % and 9.7 %, respectively. The overall incidence of adverse reactions considered as drug-related in patients treated with the combination of sitagliptin and metformin was comparable to metformin alone (14.0 % each) and greater than sitagliptin alone (6.7 %), with the differences relative to sitagliptin alone primarily due to gastrointestinal adverse reactions.

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.

No clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed with Januvia treatment.

Post-marketing Experience:
During post-marketing experience the following additional side effects have been reported (frequency not known): hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, and exfoliative skin conditions including Stevens-Johnson syndrome (see section 4.4).

4.9 Overdose

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were generally well tolerated. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. 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 dialyzable. In clinical studies, approximately 13.5 % of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: DPP-4 Inhibitor, ATC code: A10BH01.

Januvia is a member of a class of oral anti-hyperglycaemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors. The improvement in glycaemic control observed with this agent may be mediated by enhancing the levels of active incretin hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling 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 hydrolyzes 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 hemoglobin A_{1c} (HbA_{1c}) and lower fasting and postprandial glucose concentrations. The glucose-dependent mechanism of sitagliptin is distinct from the mechanism of sulphonylureas, 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.

In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Co-administration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations.

Overall, sitagliptin improved glycaemic control when given as monotherapy, when used in combination with metformin (initial or add-on therapy), in combination with a sulphonylurea (with or without metformin), in combination with a thiazolidinedione, and in combination with a thiazolidinedione and metformin, as measured by clinically relevant reductions in HbA_{1c} from baseline at study endpoint (see Table 2).

Two studies were conducted to evaluate the efficacy and safety of Januvia monotherapy. Treatment with sitagliptin at 100 mg once daily as monotherapy provided significant improvements in HbA_{1c}, fasting plasma glucose (FPG), and 2-hour post-prandial glucose (2-hour PPG), compared to placebo in two studies, one of 18- and one of 24-weeks duration. Improvement of surrogate markers of beta cell function, including HOMA-β (Homeostasis Model Assessment-β), proinsulin to insulin ratio, and measures of beta cell responsiveness from the frequently-sampled meal tolerance test were observed. The observed incidence of hypoglycaemia in patients treated with Januvia was similar to placebo. Body weight did not increase from baseline with sitagliptin therapy in either study, compared to a small reduction in patients given placebo.

In a study in patients with type 2 diabetes and chronic renal insufficiency (creatinine clearance < 50 ml/min), the safety and tolerability of reduced doses of sitagliptin were investigated and generally similar to placebo. In addition, the reductions in HbA_{1c} and FPG with sitagliptin compared to placebo were generally similar to those observed in other monotherapy studies in patients with normal renal function (see section 5.2). The number of patients with moderate to severe renal insufficiency was too low to confirm safe use of sitagliptin in this type of patients.

Sitagliptin 100 mg once daily provided significant improvements in glycaemic parameters compared with placebo in two 24-week studies of sitagliptin as add-on therapy, one in combination with metformin and one in combination with pioglitazone. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo. In these studies there was a similar incidence of hypoglycaemia reported for patients treated with sitagliptin or placebo.

A 24-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to glimepiride alone or glimepiride in combination with metformin. The addition of sitagliptin to either glimepiride alone or to glimepiride and metformin provided significant improvements in glycaemic parameters. Patients treated with sitagliptin had a modest increase in body weight compared to those given placebo.

A 54-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to the combination of rosiglitazone and metformin. The addition of sitagliptin to rosiglitazone and metformin provided significant improvements in glycaemic parameters at the primary timepoint of Week 18, with improvements sustained through the end of the study. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo (1.9 vs. 1.3 kg).

In a 24-week placebo-controlled factorial study of initial therapy, sitagliptin 50 mg twice daily in combination with metformin (500 mg or 1000 mg twice daily) provided significant improvements in glycaemic parameters compared with either monotherapy. The decrease in body weight with the combination of sitagliptin and metformin was similar to that observed with metformin alone or placebo; there was no change from baseline for patients on sitagliptin alone. The incidence of hypoglycaemia was similar across treatment groups.

Table 2. HbA_{1c} results in placebo-controlled monotherapy and combination therapy studies*

Study	Mean baseline HbA_{1c} (%)	Mean change from baseline HbA_{1c} (%)†	Placebo-corrected mean change in HbA_{1c} (%)† (95 % CI)
Monotherapy Studies			
Sitagliptin 100 mg once daily§ (N= 193)	8.0	-0.5	-0.6‡ (-0.8, -0.4)
Sitagliptin 100 mg once daily‖ (N= 229)	8.0	-0.6	-0.8‡ (-1.0, -0.6)
Combination Therapy Studies			
Sitagliptin 100 mg once daily added to ongoing metformin therapy‖ (N=453)	8.0	-0.7	-0.7‡ (-0.8, -0.5)
Sitagliptin 100 mg once daily added to ongoing pioglitazone therapy‖ (N=163)	8.1	-0.9	-0.7‡ (-0.9, -0.5)
Sitagliptin 100 mg once daily added to ongoing glimepiride therapy‖ (N=102)	8.4	-0.3	-0.6‡ (-0.8, -0.3)
Sitagliptin 100 mg once daily added to ongoing glimepiride + metformin therapy‖ (N=115)	8.3	-0.6	-0.9‡ (-1.1, -0.7)
Sitagliptin 100 mg once daily added to ongoing rosiglitazone + metformin therapy (N=170)			
Week 18	8.8	-1.0	-0.7‡ (-0.9, -0.5)
Week 54	8.8	-1.0	-0.8‡ (-1.0, -0.5)
Initial therapy (twice daily)‖: Sitagliptin 50 mg + metformin 500 mg (N=183)	8.8	-1.4	-1.6‡ (-1.8, -1.3)
Initial therapy (twice daily)‖: Sitagliptin 50 mg + metformin 1000 mg (N=178)	8.8	-1.9	-2.1‡ (-2.3, -1.8)

* 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 or placebo + combination treatment.

§ HbA_{1c} (%) at week 18.

‖ HbA_{1c} (%) at week 24.

A 24-week active (metformin)-controlled study was designed to evaluate the efficacy and safety of sitagliptin 100 mg once daily (N=528) compared to metformin (N=522) in patients with inadequate glycaemic control on diet and exercise and who were not on anti-hyperglycaemic therapy (off therapy for at least 4 months). The mean dose of metformin was approximately 1900 mg per day. The reduction in HbA_{1c} from mean baseline values of 7.2 % was -0.38 % for sitagliptin and -0.55 % for metformin. The overall incidence of gastrointestinal adverse reactions considered as drug-related in patients treated with sitagliptin was 2.7 % compared with 12.6 % in patients treated with metformin. The incidence of hypoglycaemia was not significantly different between the treatment groups

(sitagliptin, 1.3 %; metformin, 1.9 %). Body weight decreased from baseline in both groups (sitagliptin, -0.6 kg; metformin -1.9 kg).

In a study comparing the efficacy and safety of the addition of Januvia 100 mg once daily or glipizide (a sulphonylurea agent) in patients with inadequate glycaemic control on metformin monotherapy, sitagliptin was similar to glipizide in reducing HbA_{1c}. The mean glipizide dose used in the comparator group was 10 mg per day with approximately 40 % of patients requiring a glipizide dose of ≤ 5 mg/day throughout the study. However, more patients in the sitagliptin group discontinued due to lack of efficacy than in the glipizide group. 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 vs. +1.1 kg). 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 %).

5.2 Pharmacokinetic properties

Absorption
Following 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, mean plasma AUC of sitagliptin was 8.52 μM•hr, C_{max} was 950 nM. 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.

Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for C_{max} and C_{24hr} (C_{max} increased in a greater than dose-proportional manner and C_{24hr} increased in a less than dose-proportional manner).

Distribution
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 %).

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.

In vitro data showed that sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4 and CYP1A2.

Elimination
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. Sitagliptin accumulates only minimally with multiple doses. The 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. Sitagliptin is not a substrate for OCT2 or OAT1 or PEPT1/2 transporters. *In vitro*, sitagliptin did not inhibit OAT3 (IC50=160 μM) or p-glycoprotein (up to 250 μM) mediated transport at therapeutically relevant plasma concentrations. In a clinical study sitagliptin had a small effect on plasma digoxin concentrations indicating that sitagliptin may be a mild inhibitor of p-glycoprotein.

Characteristics in patients
The pharmacokinetics of sitagliptin were generally similar in healthy subjects and in patients with type 2 diabetes.

Renal insufficiency
A single-dose, open-label study was conducted to evaluate the pharmacokinetics of a reduced dose of sitagliptin (50-mg) 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 (ESRD) on hemodialysis.

Patients with mild renal insufficiency did not have a clinically meaningful increase in the plasma concentration of sitagliptin as compared to normal healthy control subjects. 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 hemodialysis, as compared to normal healthy control subjects. Sitagliptin was modestly removed by hemodialysis (13.5 % over a 3- to 4-hour hemodialysis session starting 4 hours postdose). Januvia is not recommended for use in patients with moderate or severe renal insufficiency including those with ESRD since experience in these patients is too limited. (See section 4.2.)

Hepatic insufficiency
No dosage adjustment for Januvia is necessary for patients with mild or moderate hepatic insufficiency (Child-Pugh score ≤ 9). 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.

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.

Paediatric
No studies with Januvia have been performed in paediatric patients.

Other patient characteristics
No dosage adjustment is necessary based on gender, race, or body mass index (BMI). These characteristics had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

5.3 Preclinical safety data

Renal and liver toxicity were observed in rodents at systemic exposure values 58 times the human exposure level, while the no-effect level was found at 19 times the human exposure level. Incisor teeth abnormalities were observed in rats at exposure levels 67 times the clinical exposure level; the no-effect level for this finding was 58-fold based on the 14-week rat study. The relevance of these findings for humans is unknown. Transient treatment-related physical signs, some of which suggest neural toxicity, such as open-mouth breathing, salivation, white foamy emesis, ataxia, trembling, decreased activity, and/or hunched posture were observed in dogs at exposure levels approximately

23 times the clinical exposure level. In addition, very slight to slight skeletal muscle degeneration was also observed histologically at doses resulting in systemic exposure levels of approximately 23 times the human exposure level. A no-effect level for these findings was found at an exposure 6-fold the clinical exposure level.

Sitagliptin has not been demonstrated to be genotoxic in preclinical studies. Sitagliptin was not carcinogenic in mice. In rats, there was an increased incidence of hepatic adenomas and carcinomas at systemic exposure levels 58 times the human exposure level. Since hepatotoxicity has been shown to correlate with induction of hepatic neoplasia in rats, this increased incidence of hepatic tumors in rats was likely secondary to chronic hepatic toxicity at this high dose. Because of the high safety margin (19-fold at this no-effect level), these neoplastic changes are not considered relevant for the situation in humans.

No adverse effects upon fertility were observed in male and female rats given sitagliptin prior to and throughout mating.

In a pre-/postnatal development study performed in rats sitagliptin showed no adverse effects.

Reproductive toxicity studies showed a slight treatment-related increased incidence of fetal rib malformations (absent, hypoplastic and wavy ribs) in the offspring of rats at systemic exposure levels more than 29 times the human exposure levels. Maternal toxicity was seen in rabbits at more than 29 times the human exposure levels. Because of the high safety margins, these findings do not suggest a relevant risk for human reproduction. Sitagliptin is secreted in considerable amounts into the milk of lactating rats (milk/plasma ratio: 4:1).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
microcrystalline cellulose (E460)
calcium hydrogen phosphate, anhydrous (E341)
croscarmellose sodium (E468)
magnesium stearate (E470b)
sodium stearyl fumarate

Film coating:
polyvinyl alcohol
macrogol 3350
talc (E553b)
titanium dioxide (E171)
red iron oxide (E172)
yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Opaque blisters (PVC/PE/PVDC and aluminum). Packs of 14, 28, 56, 84 or 98 film-coated tablets and 50 x 1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd.
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/383/013
EU/1/07/383/014
EU/1/07/383/015
EU/1/07/383/016
EU/1/07/383/017
EU/1/07/383/018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 March 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu