**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Januvia 25 mg film-coated tablets
Januvia 50 mg film-coated tablets
Januvia 100 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Januvia 25 mg film-coated tablets
Each tablet contains sitagliptin phosphate monohydrate, equivalent to 25 mg sitagliptin.

Januvia 50 mg film-coated tablets
Each tablet contains sitagliptin phosphate monohydrate, equivalent to 50 mg sitagliptin.

Januvia 100 mg film-coated tablets
Each tablet contains sitagliptin phosphate monohydrate, equivalent to 100 mg sitagliptin.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Januvia 25 mg film-coated tablets
Round, pink film-coated tablet with "221" on one side.

Januvia 50 mg film-coated tablets
Round, light beige film-coated tablet with "112" on one side.

Januvia 100 mg film-coated tablets
Round, beige film-coated tablet with "277" on one side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

For adult patients with type 2 diabetes mellitus, Januvia is indicated to improve glycaemic control:

as monotherapy:

- in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

as dual oral therapy in combination with:

- metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.

- 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.

- a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e. a thiazolidinedione) when use of a PPARγ agonist is appropriate and when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control.

as triple oral therapy in combination with:

- a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

- a PPARγ agonist and metformin when use of a PPARγ agonist is appropriate and when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

Januvia is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dose of insulin do not provide adequate glycaemic control.

## 4.2 Posology and method of administration

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

When Januvia is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin 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.

Special populations
*Renal impairment*
When considering the use of sitagliptin in combination with another anti-diabetic medicinal product, its conditions for use in patients with renal impairment should be checked.

For patients with mild renal impairment (glomerular filtration rate [GFR] ≥ 60 to < 90 mL/min), no dose adjustment is required.

For patients with moderate renal impairment (GFR ≥ 45 to < 60 mL/min), no dosage adjustment is required.

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

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

Because there is a dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of Januvia and periodically thereafter.

*Hepatic impairment*
No dose adjustment is necessary for patients with mild to moderate hepatic impairment. Januvia has not been studied in patients with severe hepatic impairment and care should be exercised (see section 5.2).

However, because sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetics of sitagliptin.

*Elderly*
No dose adjustment is necessary based on age.

*Paediatric population*
Sitagliptin should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy. Currently available data are described in sections 4.8, 5.1, and 5.2. Sitagliptin has not been studied in paediatric patients under 10 years of age.

Method of administration
Januvia can be taken with or without food.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see sections 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.

Acute pancreatitis
Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of sitagliptin (with or without supportive treatment), but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, Januvia and other potentially suspect medicinal products should be discontinued; if acute pancreatitis is confirmed, Januvia should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Hypoglycaemia when used in combination with other anti-hyperglycaemic medicinal products
In clinical trials of Januvia as monotherapy and as part of combination therapy with medicinal products 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. Hypoglycaemia has been observed when sitagliptin was used in combination with insulin or a sulphonylurea. Therefore, to reduce the risk of hypoglycaemia, a lower dose of sulphonylurea or insulin may be considered (see section 4.2).

Renal impairment
Sitagliptin is renally excreted. To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with GFR < 45 mL/min, as well as in ESRD patients requiring haemodialysis or peritoneal dialysis (see sections 4.2 and 5.2).

When considering the use of sitagliptin in combination with another anti-diabetic medicinal product, its conditions for use in patients with renal impairment should be checked.

Hypersensitivity reactions
Post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin 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 some reports occurring after the first dose. If a hypersensitivity reaction is

suspected, Januvia should be discontinued. Other potential causes for the event should be assessed, and alternative treatment for diabetes initiated.

Bullous pemphigoid
There have been post-marketing reports of bullous pemphigoid in patients taking DPP-4 inhibitors including sitagliptin. If bullous pemphigoid is suspected, Januvia should be discontinued.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

## 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.

*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 impairment or end-stage renal disease (ESRD). For this reason, it is possible that potent CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the pharmacokinetics of sitagliptin in patients with severe renal impairment or ESRD. The effect of potent CYP3A4 inhibitors in the setting of renal impairment has not been assessed in a clinical study.

*In vitro* transport studies showed that sitagliptin is a substrate for p-glycoprotein and organic anion transporter-3 (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*.

*Metformin:* Co-administration of multiple twice-daily doses of 1,000 mg metformin with 50 mg sitagliptin did not meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.

*Ciclosporin:* A study was conducted to assess the effect of ciclosporin, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Co-administration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of ciclosporin 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.

Effects of sitagliptin on other medicinal products
*Digoxin:* Sitagliptin had a small effect on plasma digoxin concentrations. Following administration of 0.25 mg digoxin concomitantly with 100 mg of sitagliptin 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 dose adjustment of digoxin is recommended. However, patients at risk of digoxin toxicity should be monitored for this when sitagliptin and digoxin are administered concomitantly.

*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 may be a mild inhibitor of p-glycoprotein *in vivo*.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of sitagliptin 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.

Breast-feeding
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.

Fertility
Animal data do not suggest an effect of treatment with sitagliptin on male and female fertility. Human data are lacking.

## 4.7 Effects on ability to drive and use machines

Januvia has no or negligible influence on the ability to drive and use machines. However, when driving or using machines, it should be taken into account that dizziness and somnolence have been reported.

In addition, patients should be alerted to the risk of hypoglycaemia when Januvia is used in combination with a sulphonylurea or with insulin.

## 4.8 Undesirable effects

Summary of the safety profile
Serious adverse reactions including pancreatitis and hypersensitivity reactions have been reported. Hypoglycaemia has been reported in combination with sulphonylurea (4.7 %-13.8 %) and insulin (9.6 %) (see section 4.4).

Tabulated list of adverse reactions
Adverse reactions are listed below (Table 1) by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (cannot be estimated from the available data).

**Table 1. The frequency of adverse reactions identified from placebo-controlled clinical studies of sitagliptin monotherapy and post-marketing experience**

| Adverse reaction | Frequency of adverse reaction |
|---|---|
| **Blood and lymphatic system disorders** | |
| thrombocytopenia | Rare |
| | |
| **Immune system disorders** | |
| hypersensitivity reactions including anaphylactic responses[*,†] | Frequency not known |
| | |
| **Metabolism and nutrition disorders** | |
| hypoglycaemia[†] | Common |
| | |
| **Nervous system disorders** | |
| headache | Common |
| dizziness | Uncommon |
| | |

| Adverse reaction | Frequency of adverse reaction |
|---|---|
| **Respiratory, thoracic and mediastinal disorders** | |
| interstitial lung disease* | Frequency not known |
| | |
| **Gastrointestinal disorders** | |
| constipation | Uncommon |
| vomiting* | Frequency not known |
| acute pancreatitis*,†,‡ | Frequency not known |
| fatal and non-fatal haemorrhagic and necrotizing pancreatitis*,† | Frequency not known |
| | |
| **Skin and subcutaneous tissue disorders** | |
| pruritus* | Uncommon |
| angioedema*,† | Frequency not known |
| rash*,† | Frequency not known |
| urticaria*,† | Frequency not known |
| cutaneous vasculitis*,† | Frequency not known |
| exfoliative skin conditions including Stevens-Johnson syndrome*,† | Frequency not known |
| bullous pemphigoid* | Frequency not known |
| | |
| **Musculoskeletal and connective tissue disorders** | |
| arthralgia* | Frequency not known |
| myalgia* | Frequency not known |
| back pain* | Frequency not known |
| arthropathy* | Frequency not known |
| | |
| **Renal and urinary disorders** | |
| impaired renal function* | Frequency not known |
| acute renal failure* | Frequency not known |

*Adverse reactions were identified through post-marketing surveillance.
† See section 4.4.
‡ See *TECOS Cardiovascular Safety Study* below.

Description of selected adverse reactions
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 sitagliptin 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 sitagliptin (not reaching the 5 % level, but occurring with an incidence of > 0.5 % higher with sitagliptin than that in the control group) included osteoarthritis and pain in extremity.

Some adverse reactions were observed more frequently in studies of combination use of sitagliptin with other anti-diabetic medicinal products than in studies of sitagliptin monotherapy. These included hypoglycaemia (frequency very common with the combination of sulphonylurea and metformin), influenza (common with insulin (with or without metformin)), nausea and vomiting (common with metformin), flatulence (common with metformin or pioglitazone), constipation (common with the combination of sulphonylurea and metformin), peripheral oedema (common with pioglitazone or the combination of pioglitazone and metformin), somnolence and diarrhoea (uncommon with metformin), and dry mouth (uncommon with insulin (with or without metformin)).

Paediatric population
In clinical trials with sitagliptin in paediatric patients with type 2 diabetes mellitus aged 10 to17 years, the profile of adverse reactions was comparable to that observed in adults.

*TECOS Cardiovascular Safety Study*
The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7,332 patients treated with sitagliptin, 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and < 50 mL/min/1.73 $m^2$), and 7,339 patients treated with placebo in the intention-to-treat population. Both treatments were added to usual care targeting regional standards for $HbA_{1c}$ and CV risk factors. The overall incidence of serious adverse events in patients receiving sitagliptin was similar to that in patients receiving placebo.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were administered. 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 clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

Sitagliptin is modestly dialysable. In clinical studies, approximately 13.5 % of the dose was removed over a 3- to 4-hour haemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

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

Mechanism of action
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 medicinal product 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 haemoglobin $A_{1c}$ ($HbA_{1c}$) 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.

Clinical efficacy and safety

Overall, sitagliptin improved glycaemic control when used as monotherapy or in combination treatment in adult patients with type 2 diabetes (see Table 2).

Two studies were conducted to evaluate the efficacy and safety of sitagliptin 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 sitagliptin 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.

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 26-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to the combination of pioglitazone and metformin. The addition of sitagliptin to pioglitazone and metformin provided significant improvements in glycaemic parameters. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo. The incidence of hypoglycaemia was also similar in 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 insulin (at a stable dose for at least 10 weeks) with or without metformin (at least 1,500 mg). In patients taking pre-mixed insulin, the mean daily dose was 70.9 U/day. In patients taking non-pre-mixed (intermediate/long-acting) insulin, the mean daily dose was 44.3 U/day. The addition of sitagliptin to insulin provided significant improvements in glycaemic parameters. There was no meaningful change from baseline in body weight in either group.

In a 24-week placebo-controlled factorial study of initial therapy, sitagliptin 50 mg twice daily in combination with metformin (500 mg or 1,000 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 pioglitazone + metformin therapy# (N=152) | 8.8 | -1.2 | -0.7‡ (-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 1,000 mg (N=178) | 8.8 | -1.9 | -2.1‡ (-2.3, -1.8) |
| Sitagliptin 100 mg once daily added to ongoing insulin (+/- metformin) therapy‖ (N=305) | 8.7 | -0.6¶ | -0.6‡,¶ (-0.7, -0.4) |

* 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.
# $HbA_{1c}$ (%) at week 26.
¶ Least squares mean adjusted for metformin use at Visit 1 (yes/no), insulin use at Visit 1 (pre-mixed vs. non-pre-mixed [intermediate- or long-acting]), and baseline value. Treatment by stratum (metformin and insulin use) interactions were not significant ($p > 0.10$).

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 1,900 mg per day. The reduction in $HbA_{1c}$ from mean baseline values of 7.2 % was -0.43 % for sitagliptin and -0.57 % for metformin (Per Protocol Analysis). 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 sitagliptin 100 mg once daily or glipizide (a sulphonylurea) 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 %).

A 24-week placebo-controlled study involving 660 patients was designed to evaluate the insulin-sparing efficacy and safety of sitagliptin (100 mg once daily) added to insulin glargine with or without metformin (at least 1,500 mg) during intensification of insulin therapy. Baseline $HbA_{1c}$ was 8.74 % and baseline insulin dose was 37 IU/day. Patients were instructed to titrate their insulin glargine dose based on fingerstick fasting glucose values. At Week 24, the increase in daily insulin dose was 19 IU/day in patients treated with sitagliptin and 24 IU/day in patients treated with placebo. The reduction in $HbA_{1c}$ in patients treated with sitagliptin and insulin (with or without metformin) was -1.31 % compared to -0.87 % in patients treated with placebo and insulin (with or without metformin), a difference of -0.45 % [95 % CI: -0.60, -0.29]. The incidence of hypoglycaemia was 25.2 % in patients treated with sitagliptin and insulin (with or without metformin) and 36.8 % in patients treated with placebo and insulin (with or without metformin). The difference was mainly due to a higher percentage of patients in the placebo group experiencing 3 or more episodes of hypoglycaemia (9.4 vs. 19.1 %). There was no difference in the incidence of severe hypoglycaemia.

A study comparing sitagliptin at 25 or 50 mg once daily to glipizide at 2.5 to 20 mg/day was conducted in patients with moderate to severe renal impairment. This study involved 423 patients with chronic renal impairment (estimated glomerular filtration rate < 50 mL/min). After 54 weeks, the mean reduction from baseline in $HbA_{1c}$ was -0.76 % with sitagliptin and -0.64 % with glipizide (Per-Protocol Analysis). In this study, the efficacy and safety profile of sitagliptin at 25 or 50 mg once daily was generally similar to that observed in other monotherapy studies in patients with normal renal function. The incidence of hypoglycaemia in the sitagliptin group (6.2 %) was significantly lower than that in the glipizide group (17.0 %). There was also a significant difference between groups with respect to change from baseline body weight (sitagliptin -0.6 kg; glipizide +1.2 kg).

Another study comparing sitagliptin at 25 mg once daily to glipizide at 2.5 to 20 mg/day was conducted in 129 patients with ESRD who were on dialysis. After 54 weeks, the mean reduction from baseline in $HbA_{1c}$ was -0.72 % with sitagliptin and -0.87 % with glipizide. In this study, the efficacy and safety profile of sitagliptin at 25 mg once daily was generally similar to that observed in other monotherapy studies in patients with normal renal function. The incidence of hypoglycaemia was not significantly different between the treatment groups (sitagliptin, 6.3 %; glipizide, 10.8 %).

In another study involving 91 patients with type 2 diabetes and chronic renal impairment (creatinine clearance < 50 mL/min), the safety and tolerability of treatment with sitagliptin at 25 or 50 mg once daily were generally similar to placebo. In addition, after 12 weeks, the mean reductions in $HbA_{1c}$ (sitagliptin -0.59 %; placebo -0.18 %) and FPG (sitagliptin -25.5 mg/dL; placebo -3.0 mg/dL) were generally similar to those observed in other monotherapy studies in patients with normal renal function (see section 5.2).

The TECOS was a randomised study in 14,671 patients in the intention-to-treat population with an $HbA_{1c}$ of ≥ 6.5 to 8.0 % with established CV disease who received sitagliptin (7,332) 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and < 50 mL/min/1.73 $m^2$) or placebo (7,339) added to usual care targeting regional standards for $HbA_{1c}$ and CV risk factors. Patients with an eGFR < 30 mL/min/1.73 $m^2$ were not to be enrolled in the study. The study population included 2,004 patients ≥ 75 years of age and 3,324 patients with renal impairment (eGFR < 60 mL/min/1.73 $m^2$).

Over the course of the study, the overall estimated mean (SD) difference in $HbA_{1c}$ between the sitagliptin and placebo groups was 0.29 % (0.01), 95 % CI (-0.32, -0.27); p < 0.001.

The primary cardiovascular endpoint was a composite of the first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for unstable angina. Secondary cardiovascular endpoints included the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; first occurrence of the individual components of the primary composite; all-cause mortality; and hospital admissions for congestive heart failure.

After a median follow up of 3 years, sitagliptin, when added to usual care, did not increase the risk of major adverse cardiovascular events or the risk of hospitalisation for heart failure compared to usual care without sitagliptin in patients with type 2 diabetes (Table 3).

**Table 3. Rates of Composite Cardiovascular Outcomes and Key Secondary Outcomes**

| | **Sitagliptin 100 mg** | | **Placebo** | | | |
|---|---|---|---|---|---|---|
| | **N (%)** | **Incidence rate per 100 patient-years*** | **N (%)** | **Incidence rate per 100 patient-years*** | **Hazard Ratio (95% CI)** | **p-value†** |
| **Analysis in the Intention-to-Treat Population** | | | | | | |
| **Number of patients** | **7,332** | | **7,339** | | | |
| **Primary Composite Endpoint** (Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for unstable angina) | 839 (11.4) | 4.1 | 851 (11.6) | 4.2 | 0.98 (0.89–1.08) | <0.001 |
| **Secondary Composite Endpoint** (Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) | 745 (10.2) | 3.6 | 746 (10.2) | 3.6 | 0.99 (0.89–1.10) | <0.001 |
| **Secondary Outcome** | | | | | | |
| Cardiovascular death | 380 (5.2) | 1.7 | 366 (5.0) | 1.7 | 1.03 (0.89-1.19) | 0.711 |
| All myocardial infarction (fatal and non-fatal) | 300 (4.1) | 1.4 | 316 (4.3) | 1.5 | 0.95 (0.81–1.11) | 0.487 |
| All stroke (fatal and non-fatal) | 178 (2.4) | 0.8 | 183 (2.5) | 0.9 | 0.97 (0.79–1.19) | 0.760 |
| Hospitalisation for unstable angina | 116 (1.6) | 0.5 | 129 (1.8) | 0.6 | 0.90 (0.70–1.16) | 0.419 |
| Death from any cause | 547 (7.5) | 2.5 | 537 (7.3) | 2.5 | 1.01 (0.90–1.14) | 0.875 |
| Hospitalisation for heart failure‡ | 228 (3.1) | 1.1 | 229 (3.1) | 1.1 | 1.00 (0.83–1.20) | 0.983 |

* Incidence rate per 100 patient-years is calculated as 100 × (total number of patients with ≥ 1 event during eligible exposure period per total patient-years of follow-up).

† Based on a Cox model stratified by region. For composite endpoints, the p-values correspond to a test of non-inferiority seeking to show that the hazard ratio is less than 1.3. For all other endpoints, the p-values correspond to a test of differences in hazard rates.

‡ The analysis of hospitalisation for heart failure was adjusted for a history of heart failure at baseline.

Paediatric population
A 54-week, double-blind study was conducted to evaluate the efficacy and safety of sitagliptin 100 mg once daily in paediatric patients (10 to 17 years of age) with type 2 diabetes who were not on anti-hyperglycaemic therapy for at least 12 weeks (with HbA1c 6.5% to 10%) or were on a stable dose of insulin for at least 12 weeks (with HbA1c 7% to 10%). Patients were randomised to sitagliptin 100 mg once daily or placebo for 20 weeks.

Mean baseline HbA1c was 7.5%. Treatment with sitagliptin 100 mg did not provide significant improvement in HbA1c at 20 weeks. The reduction in HbA1c in patients treated with sitagliptin (N=95) was 0.0% compared to 0.2% in patients treated with placebo (N=95), a difference of -0.2% (95% CI: -0.7, 0.3). See section 4.2.

## 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 co-administration of a high-fat meal with sitagliptin 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 litres. The fraction of sitagliptin reversibly bound to plasma proteins is low (38 %).

Biotransformation
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, ciclosporin, 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 impairment*
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 impairment compared to normal healthy control subjects. The study included patients with mild, moderate, and severe renal impairment, as well as patients with ESRD on haemodialysis. In addition, the effects of renal impairment on sitagliptin pharmacokinetics in patients with type 2 diabetes and mild, moderate, or severe renal impairment (including ESRD) were assessed using population pharmacokinetic analyses.

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

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

*Hepatic impairment*
No dose adjustment for Januvia is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score ≤ 9). There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score > 9). However, because sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetics of sitagliptin.

*Elderly*
No dose 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 population*
The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in paediatric patients (10 to 17 years of age) with type 2 diabetes. In this population, the dose-adjusted AUC of sitagliptin in plasma was approximately 18 % lower compared to adult patients with type 2 diabetes for a 100 mg dose. This is not considered to be a clinically meaningful difference compared to adult patients based on the flat PK/PD relationship between the dose of 50 mg and 100 mg. No studies with sitagliptin have been performed in paediatric patients with age <10 years.

*Other patient characteristics*
No dose 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 tumours 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 foetal 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
propyl gallate

Film coating:
poly(vinyl 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

2 years

## 6.4 Special precautions for storage

Store below 25 °C.

## 6.5 Nature and contents of container

Opaque blisters (PVC/PE/PVDC and aluminium). Packs of 14, 28, 30, 56, 84, 90 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 medicinal product or waste material should be disposed of in accordance with local requirements.

# 7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

# 8. MARKETING AUTHORISATION NUMBER(S)

Januvia 25 mg film-coated tablets
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
EU/1/07/383/019
EU/1/07/383/020

Januvia 50 mg film-coated tablets
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
EU/1/07/383/021
EU/1/07/383/022

Januvia 100 mg film-coated tablets
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
EU/1/07/383/023
EU/1/07/383/024

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 March 2007
Date of latest renewal: 23 February 2012

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Januvia 25 mg film-coated tablets
sitagliptin

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
56 film-coated tablets
84 film-coated tablets
90 film-coated tablets
98 film-coated tablets
50 x 1 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store below 25 °C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/383/001 14 film-coated tablets
EU/1/07/383/002 28 film-coated tablets
EU/1/07/383/019 30 film-coated tablets
EU/1/07/383/003 56 film-coated tablets
EU/1/07/383/004 84 film-coated tablets
EU/1/07/383/020 90 film-coated tablets
EU/1/07/383/005 98 film-coated tablets
EU/1/07/383/006 50 x 1 film-coated tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Januvia 25 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS**

## 1. NAME OF THE MEDICINAL PRODUCT

Januvia 25 mg tablets
sitagliptin

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

MSD

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Januvia 50 mg film-coated tablets
sitagliptin

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
56 film-coated tablets
84 film-coated tablets
90 film-coated tablets
98 film-coated tablets
50 x 1 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store below 25 °C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/383/007 14 film-coated tablets
EU/1/07/383/008 28 film-coated tablets
EU/1/07/383/021 30 film-coated tablets
EU/1/07/383/009 56 film-coated tablets
EU/1/07/383/010 84 film-coated tablets
EU/1/07/383/022 90 film-coated tablets
EU/1/07/383/011 98 film-coated tablets
EU/1/07/383/012 50 x 1 film-coated tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Januvia 50 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS**

## 1. NAME OF THE MEDICINAL PRODUCT

Januvia 50 mg tablets
sitagliptin

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

MSD

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Januvia 100 mg film-coated tablets
sitagliptin

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
56 film-coated tablets
84 film-coated tablets
90 film-coated tablets
98 film-coated tablets
50 x 1 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store below 25 °C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/383/013 14 film-coated tablets
EU/1/07/383/014 28 film-coated tablets
EU/1/07/383/023 30 film-coated tablets
EU/1/07/383/015 56 film-coated tablets
EU/1/07/383/016 84 film-coated tablets
EU/1/07/383/024 90 film-coated tablets
EU/1/07/383/017 98 film-coated tablets
EU/1/07/383/018 50 x 1 film-coated tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Januvia 100 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS**

## 1. NAME OF THE MEDICINAL PRODUCT

Januvia 100 mg tablets
sitagliptin

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

MSD

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

# B. PACKAGE LEAFLET

**Package leaflet: Information for the patient**

**Januvia 25 mg film-coated tablets**
**Januvia 50 mg film-coated tablets**
**Januvia 100 mg film-coated tablets**
sitagliptin

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**


1. What Januvia is and what it is used for
2. What you need to know before you take Januvia
3. How to take Januvia
4. Possible side effects
5. How to store Januvia
6. Contents of the pack and other information


## 1. What Januvia is and what it is used for

Januvia contains the active substance sitagliptin which is a member of a class of medicines called DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors) that lowers blood sugar levels in adult patients with type 2 diabetes mellitus.

This medicine helps to increase the levels of insulin produced after a meal and decreases the amount of sugar made by the body.

Your doctor has prescribed this medicine to help lower your blood sugar, which is too high because of your type 2 diabetes. This medicine can be used alone or in combination with certain other medicines (insulin, metformin, sulphonylureas, or glitazones) that lower blood sugar, which you may already be taking for your diabetes together with a food and exercise plan.

What is type 2 diabetes?
Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems like heart disease, kidney disease, blindness, and amputation.

## 2. What you need to know before you take Januvia

**Do not take Januvia**
- if you are allergic to sitagliptin or any of the other ingredients of this medicine (listed in section 6).

**Warnings and precautions**
Cases of inflammation of the pancreas (pancreatitis) have been reported in patients receiving Januvia (see section 4).

If you encounter blistering of the skin it may be a sign for a condition called bullous pemphigoid. Your doctor may ask you to stop Januvia.

Tell your doctor if you have or have had:
- a disease of the pancreas (such as pancreatitis)
- gallstones, alcohol dependence or very high levels of triglycerides (a form of fat) in your blood. These medical conditions can increase your chance of getting pancreatitis (see section 4).
- type 1 diabetes
- diabetic ketoacidosis (a complication of diabetes with high blood sugar, rapid weight loss, nausea or vomiting)
- any past or present kidney problems
- an allergic reaction to Januvia (see section 4)

This medicine is unlikely to cause low blood sugar because it does not work when your blood sugar is low. However, when this medicine is used in combination with a sulphonylurea medicine or with insulin, low blood sugar (hypoglycaemia) can occur. Your doctor may reduce the dose of your sulphonylurea or insulin medicine.

**Children and adolescents**
Children and adolescents below 18 years should not use this medicine. It is not effective in children and adolescents between the ages of 10 and 17 years. It is not known if this medicine is safe and effective when used in children younger than 10 years.

**Other medicines and Januvia**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor if you are taking digoxin (a medicine used to treat irregular heartbeat and other heart problems). The level of digoxin in your blood may need to be checked if taking with Januvia.

**Pregnancy and breast-feeding**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
You should not take this medicine during pregnancy.

It is not known if this medicine passes into breast milk. You should not take this medicine if you are breast-feeding or plan to breast-feed.

**Driving and using machines**
This medicine has no or negligible influence on the ability to drive and use machines. However, dizziness and drowsiness have been reported, which may affect your ability to drive or use machines.

Taking this medicine in combination with medicines called sulphonylureas or with insulin can cause hypoglycaemia, which may affect your ability to drive and use machines or work without safe foothold.

**Januvia contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

## 3. How to take Januvia

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The usual recommended dose is:
– one 100 mg film-coated tablet
– once a day
– by mouth

If you have kidney problems, your doctor may prescribe lower doses (such as 25 mg or 50 mg).

You can take this medicine with or without food and drink.

Your doctor may prescribe this medicine alone or with certain other medicines that lower blood sugar.

Diet and exercise can help your body use its blood sugar better. It is important to stay on the diet and exercise recommended by your doctor while taking Januvia.

**If you take more Januvia than you should**
If you take more than the prescribed dosage of this medicine, contact your doctor immediately.

**If you forget to take Januvia**
If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take a double dose of this medicine.

**If you stop taking Januvia**
Continue to take this medicine as long as your doctor prescribes it so you can continue to help control your blood sugar. You should not stop taking this medicine without talking to your doctor first.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

STOP taking Januvia and contact a doctor immediately if you notice any of the following serious side effects:
- Severe and persistent pain in the abdomen (stomach area) which might reach through to your back with or without nausea and vomiting, as these could be signs of an inflamed pancreas (pancreatitis).

If you have a serious allergic reaction (frequency not known), including rash, hives, blisters on the skin/peeling skin and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing, stop taking this medicine and call your doctor right away. Your doctor may prescribe a medicine to treat your allergic reaction and a different medicine for your diabetes.

Some patients have experienced the following side effects after adding sitagliptin to metformin:
Common (may affect up to 1 in 10 people): low blood sugar, nausea, flatulence, vomiting
Uncommon (may affect up to 1 in 100 people): stomach ache, diarrhoea, constipation, drowsiness

Some patients have experienced different types of stomach discomfort when starting the combination of sitagliptin and metformin together (frequency is common).

Some patients have experienced the following side effects while taking sitagliptin in combination with a sulphonylurea and metformin:
Very common (may affect more than 1 in 10 people): low blood sugar
Common: constipation

Some patients have experienced the following side effects while taking sitagliptin and pioglitazone:
Common: flatulence, swelling of the hands or legs

Some patients have experienced the following side effects while taking sitagliptin in combination with pioglitazone and metformin:
Common: swelling of the hands or legs

Some patients have experienced the following side effects while taking sitagliptin in combination with insulin (with or without metformin):
Common: flu
Uncommon: dry mouth

Some patients have experienced the following side effects while taking sitagliptin alone in clinical studies, or during post-approval use alone and/or with other diabetes medicines:
Common: low blood sugar, headache, upper respiratory infection, stuffy or runny nose and sore throat, osteoarthritis, arm or leg pain
Uncommon: dizziness, constipation, itching
Rare: reduced number of platelets
Frequency not known: kidney problems (sometimes requiring dialysis), vomiting, joint pain, muscle pain, back pain, interstitial lung disease, bullous pemphigoid (a type of skin blister)

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Januvia

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and the carton after 'EXP'. The expiry date refers to the last day of that month.

Store below 25 °C.

Do not throw away medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Januvia contains**
- The active substance is sitagliptin:
  - Each Januvia 25 mg film-coated tablet (tablet) contains sitagliptin phosphate monohydrate, equivalent to 25 mg sitagliptin.
  - Each Januvia 50 mg film-coated tablet (tablet) contains sitagliptin phosphate monohydrate, equivalent to 50 mg sitagliptin.
  - Each Januvia 100 mg film-coated tablet (tablet) contains sitagliptin phosphate monohydrate, equivalent to 100 mg sitagliptin.

- The other ingredients are:
  - Tablet core: microcrystalline cellulose (E460), calcium hydrogen phosphate, anhydrous (E341), croscarmellose sodium (E468), magnesium stearate (E470b), sodium stearyl fumarate and propyl gallate.

- Film coating: poly(vinyl alcohol), macrogol 3350, talc (E553b), titanium dioxide (E171), red iron oxide (E172), and yellow iron oxide (E172).

**What Januvia looks like and contents of the pack**
- Januvia 25 mg film-coated tablets are round, pink film-coated tablets with “221” on one side.
- Januvia 50 mg film-coated tablets are round, light beige film-coated tablets with “112” on one side.
- Januvia 100 mg film-coated tablets are round, beige film-coated tablets with “277” on one side.

Opaque blisters (PVC/PE/PVDC and aluminium). Packs of 14, 28, 30, 56, 84, 90 or 98 film-coated tablets and 50 x 1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.