Summary of Product Characteristic

1 Name of the medicinal product

Product Name : PANSIPTIN 100 (Sitagliptin Tablets 100 mg)

1.1 Strength : 100 mg

1.2 Pharmaceutical Dosage Form : Film coated Tablets

2 Quality and Quantitative composition

Components	Reference Standard [1]	Function	Dosage per tablet (25 mg)	Dosage per tablet (50 mg)	Dosage per tablet (100 mg)
Active substance					
Sitagliptin HCl monohydrate (Sitagliptin base)	In-house	Active ingredient	28.34 mg [2] (25.00 mg)	56.69 mg [2] (50.00 mg)	113.37 mg [2] (100.00 mg)
Intragranular Excipients					
Calcium phosphate dibasic anhydrous	Ph. Eur.	Diluent	31.08 mg	62.16 mg	124.32 mg
Microcrystalline cellulose (E460)	Ph. Eur.	Diluent	31.08 mg	62.15 mg	124.31 mg
Croscarmellose sodium (E468)	Ph. Eur.	Disintegrating agent	5.0 mg	10.0 mg	20.0 mg
Silica colloidal anhydrous	Ph. Eur.	Glidant	1.0 mg	2.0 mg	4.0 mg
Sodium stearyl fumarate	Ph. Eur.	Lubricant	2.5 mg	5.0 mg	10.0 mg
Extragranular Excipients					
Magnesium stearate (E470b)	Ph. Eur.	Lubricant	1.0 mg	2.0 mg	4.0 mg
TOTAL CORE	NA	NA	**100.0 mg**	**200.0 mg**	**400.0 mg**
Coating agent					
Ready-to-use film-coating agent	In-house	Coating agent	4.0 mg [4]	8.0 mg [4]	16.0 mg [4]
Purified Water [3]	Ph. Eur.	Solvent	q.s.	q.s.	q.s.
TOTAL TABLET	NA	NA	**104.0 mg**	**208.0 mg**	**416.0 mg**

(1) Current edition applies.
(2) Theoretical quantity of Sitagliptin HCl monohydrate. The amount is adjusted according to assay.
(3) It is evaporated during the process.
(4) 4 % w/w weight gain.
q.s: *Quantum satis*

3 Pharmaceutical Form

Round, beige film-coated tablet.

4 Clinical Particulars

4.1 Therapeutic indications

Sitagliptin is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus.

Important Limitations of Use

Sitagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

Sitagliptin has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Sitagliptin.

4.2 Posology and method of administration

Route of administration: For Oral use.

Posology

Recommended Dosing

The recommended dose of Sitagliptin is 100 mg once daily. Sitagliptin can be taken with or without food.

Recommendations For Use In Renal Impairment

For patients with an estimated glomerular filtration rate [eGFR] greater than or equal to 45 mL/min/1.73 m^2 to less than 90 mL/min/1.73 m^2, no dosage adjustment for Sitagliptin is required.

For patients with moderate renal impairment (eGFR greater than or equal to 30 mL/min/1.73 m^2 to less than 45 mL/min/1.73 m^2), the dose of JANUVIA is 50 mg once daily.

For patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) or with end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis, the dose of Sitagliptin is 25 mg once daily. Sitagliptin may be administered without regard to the timing of dialysis.

Because there is a need for dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of Sitagliptin and periodically thereafter. There have

been postmarketing reports of worsening renal function in patients with renal impairment, some of whom were prescribed inappropriate doses of sitagliptin.

Method of administration

Orally With Water.

4.3 Contraindications

History of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema.

4.4 Special warning and precautions for use

Pancreatitis

There have been reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking Sitagliptin. After initiation of sitagliptin, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, sitagliptin should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using sitagliptin.

Heart Failure

An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

Consider the risks and benefits of sitagliptin prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of sitagliptin.

Assessment of Renal Function

Assessment of renal function is recommended prior to initiating sitagliptin and periodically thereafter. A dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with ESRD requiring hemodialysis or peritoneal dialysis. Caution should be used to ensure that the correct dose of sitagliptin is prescribed for patients with moderate (eGFR ≥30 mL/min/1.73 m2 to <45 mL/min/1.73 m2) or severe (eGFR <30 mL/min/1.73 m2) renal impairment.

There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. A subset of these reports involved patients with renal insufficiency, some of whom were prescribed inappropriate doses of sitagliptin. A return to baseline levels of renal insufficiency has been observed with supportive treatment and discontinuation of potentially causative agents. Consideration can be given to cautiously reinitiating sitagliptin if another etiology is deemed likely to have precipitated the acute worsening of renal function.

Sitagliptin has not been found to be nephrotoxic in preclinical studies at clinically relevant doses, or in clinical trials.

Use with Medications Known to Cause Hypoglycemia

When sitagliptin was used in combination with a sulfonylure or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia.

Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin. 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 sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue sitagliptin, assess for other potential causes for the event, and institute alternative treatment for diabetes.

Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with sitagliptin.

Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

Bullous Pemphigoid

Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving sitagliptin. If bullous pemphigoid is suspected, sitagliptin should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with sitagliptin.

4.5 Interaction with other medicinal products and other forms of interactions

<u>Summary of the safety profile</u>

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 %).

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
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 *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.

4.6 Pregnancy and lactation

Pregnancy

Pregnancy Category B

There are no adequate data from the use of Sitagliptin in pregnant women. The potential risk for humans is unknown. Due to lack of human data, sitagliptin 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. Sitagliptin 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.

Pediatric Use

Safety and effectiveness of Sitagliptin in pediatric patients under 18 years of age have not been established.

Geriatric Use

Sitagliptin drug is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly, and it may be useful to assess renal function in these patients prior to initiating dosing and periodically thereafter.

4.7 Effects on ability to drive and use machine

This medicine has no known 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.

4.8 Undesirable effects

DRUG INTERACTIONS

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 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.

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 phamacokinetics of sitagliptin in patients with severe renal impairment or ESRD. The effects 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*.

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 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.

4.9Management of overdose

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 as dictated by the patient's clinical status.

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

Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by Sitagliptin, thereby increasing and prolonging the action of these 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. These hormones are rapidly inactivated by the enzyme, DPP-4. 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. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, Sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity *in vitro* at concentrations approximating those from therapeutic doses.

Pharmacokinetics

The pharmacokinetics of sitagliptin have been extensively characterized in healthy subjects and patients with type 2 diabetes mellitus. Following a single oral 100-mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 μM•hr, Cmax was 950 nM, and apparent terminal half-life ($t_{1/2}$) was 12.4 hours. Plasma AUC of sitagliptin increased in a dose-proportional manner and increased approximately 14% following 100 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of sitagliptin was generally similar in healthy subjects and in patients with type 2 diabetes mellitus.

Absorption

After oral administration of a 100 mg dose to healthy subjects, sitagliptin was rapidly absorbed with peak plasma concentrations (median Tmax) occurring 1 to 4 hours postdose. The absolute bioavailability of sitagliptin is approximately 87%.

Effect Of Food

Coadministration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics of sitagliptin.

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%).

Elimination

Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. The apparent terminal $t_{1/2}$ following a 100 mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min.

Metabolism

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.

Excretion

Following administration of an oral [^{14}C]sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing.

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.

5.3 Preclinical safety Data

Not available.

6 Pharmaceutical Particulars

6.1 List of excipients

Pansiptin 25 , 50 and 100

Tablet core:

Calcium phosphate dibasic anhydrous

Microcrystalline cellulose (E460)

Croscarmellose sodium (E468)

Silica colloidal anhydrous

Sodium stearyl fumarate

Magnesium stearate (E470b)

Film coating:

Polyvinyl alcohol partially hydrolized (E1203)

Titanium dioxide (E171)

Macrogol/PEG (E1521)

Talc (E553b)

Iron oxide yellow (E172)

Iron oxide red (E172)

Iron oxide black (E172) (Only For 25 mg)

6.2 Incompatibilities

Not available.

6.3 Shelf-life

36 months

6.4 Special precautions for storage

Keep out of reach of children.

Protect from light and moisture.

Store below 30ºC and in a dry place.

6.5 Nature and contents of container

Carton contain 2 blister of 14 Tablets each with pack insert.

6.6 Special precautions for disposal and other handling

---

7 Marketing Authorization Holder

Mega Lifesciences (Australia) Pty Ltd

Victoria 3810 , Australia

8. Marketing Authorization Numbers

---

9 Date of first authorization/ renewal of the authorization

---

10 Date of revision of the text