PROFESSIONAL INFORMATION

SCHEDULING STATUS S3

1 NAME OF THE MEDICINE

JOSISITIN 25 mg (film-coated tablet)

JOSISITIN 50 mg (film-coated tablet)

JOSISITIN 100 mg (film-coated tablet)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each JOSISITIN 25 mg (film-coated tablet) contains sitagliptin phosphate monohydrate equivalent to 25 mg sitagliptin.

Each JOSISITIN 50 mg (film-coated tablet) contains sitagliptin phosphate monohydrate equivalent to 50 mg sitagliptin.

Each JOSISITIN 100 mg (film-coated tablet) contains sitagliptin phosphate monohydrate equivalent to 100 mg sitagliptin.

JOSISITIN is sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

JOSISITIN 25 mg (film-coated tablet).

Dark pink, round, biconvex film coated tablet debossed with “SN” on one side and “25” on the other side.

JOSISITIN 50 mg (film-coated tablet).

Pink, round, biconvex film coated tablet debossed with “SN” on one side and “50” on the other side.

JOSISITIN 100 mg (film-coated tablet).

Brown, round, biconvex film coated tablet debossed with “SN” on one side and “100” on the other side.

4 CLINICAL PARTICULARS

4.1. Therapeutic indications

Monotherapy:

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

Combination therapy:

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

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

4.2. Posology and method of administration

Posology:

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

Special populations:

Renal impairment:

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

For patients with moderate renal insufficiency (CrCl ≥ 30 to < 50 ml/min, approximately corresponding to serum creatinine levels of > 150 µmol/litre to ≤ 265 µmol/litre in men and > 133 µmol/litre to ≤ 221 µmol/litre in women), the dose of JOSISITIN is 50 mg once daily. The dose should be decreased if CrCl decreases to < 30 ml/min.

For patients with severe renal insufficiency (CrCl < 30 ml/min, approximately corresponding to serum

creatinine levels of > 265 µmol/litre in men and > 221 µmol/litre in women), or with end-stage renal disease requiring haemodialysis, the dose of JOSISITIN is 25 mg once daily.

JOSISITIN may be administered without regard to the timing of haemodialysis.

Hepatic impairment:

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

Elderly:

No dosage adjustment is necessary for elderly patients.

Paediatric Population:

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

Method of administration:

For oral use.

JOSISITIN can be taken with or without food.

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

4.3 Contraindications

JOSISITIN is contraindicated in patients who are hypersensitive to sitagliptin or to any of the excipients listed in section 6.1.

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

JOSISITIN has not been studied in patients with severe hepatic insufficiency (see section 5.2 “Hepatic Impairment”).

4.4 Special warnings and precautions for use

General:

JOSISITIN should not be used in patients with type 1 diabetes and must not be used 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, JOSISITIN and other potentially suspect medicines should be discontinued; if acute pancreatitis is confirmed, JOSISITIN should not be restarted.

Caution should be exercised in patients with a history of pancreatitis.

Hypoglycaemia when used in combination with other anti-hyperglycaemic medicines:

In clinical trials of sitagliptin as contained in JOSISITIN as monotherapy and as part of combination therapy with medicines 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 End Stage Renal Disease (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 medicine, 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, JOSISITIN 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, JOSISITIN should be discontinued.

Sodium:

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

4.5. Interaction with other medicines and other forms of interaction

Effects of other medicines on sitagliptin:

Clinical data described below suggest that the risk for clinically meaningful interactions by co-administered medicines 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 medicines:

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. The potential risk for humans is unknown. Due to lack of human data, JOSISITIN should not be used during pregnancy.

Breastfeeding:

It is unknown whether sitagliptin is excreted in human breast milk. Animal studies have shown excretion of sitagliptin in breast milk. JOSISITIN 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

JOSISITIN 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 JOSISITIN 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 and insulin (see section 4.4).

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

System Organ Class	Frequent	Less frequent	Frequency Unknown
Blood and Lymphatic System Disorders		Thrombocytopenia	
Immune System Disorders			Hypersensitivity reactions including anaphylactic responses*,†
Metabolism and Nutrition Disorders	Hypoglycaemia†		
Nervous System Disorders	Headache	Dizziness, somnolence	
Respiratory, Thoracic and			Interstitial lung disease*

Mediastinal Disorders			
Gastrointestinal Disorders	Nausea, flatulence	Constipation, diarrhoea, upper abdominal pain	Vomiting*, acute pancreatitis*,† fatal and non-fatal haemorrhagic and necrotising pancreatitis*,†
Skin and Subcutaneous Tissue Disorders		Pruritus	Angioedema*,† rash*,† urticaria*,† cutaneous vasculitis*,† exfoliative skin conditions including Stevens-Johnson syndrome*,† bullous pemphigoid*
Musculoskeletal and connective tissue disorders			Arthralgia* myalgia* back pain* arthropathy*
Renal and Urinary Disorders			Impaired renal function* acute renal failure*
Investigations		Decreased blood glucose levels	
General disorders	Peripheral oedema		

*Adverse reactions were identified through post-marketing surveillance.

† See section 4.4.

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 antidiabetic medicines 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)).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.
Suspected adverse reactions can also be reported directly to the HCR via Patientsafety.sacg@novartis.com.

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. 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

Category and class: A.21.2 Oral Hypoglycaemics
Pharmacotherapeutic group: Medicines used in diabetes, Dipeptidyl peptidase 4 (DPP-4) inhibitors, ATC code: A10BH01.

Mechanism of action:

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

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

5.2. Pharmacokinetic properties

The pharmacokinetics of sitagliptin have been extensively characterised in healthy subjects and patients with type 2 diabetes. After oral administration of a 100 mg dose to healthy subjects, sitagliptin was absorbed with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose.

Plasma Area Under the Curve (AUC) of sitagliptin increased in a dose-proportional manner. Following a single oral 100 mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8,52 micromolar hours, C_{max} was 950 nanomol and apparent terminal half-life ($t_{½}$) was 12,4 hours. Plasma AUG of sitagliptin increased approximately 14 % following 100 mg doses at steady-state compared to the first dose. The intrasubject and inter-subject coefficients of variation for sitagliptin AUC were small (5,8 % and 15,1 %). The pharmacokinetics of sitagliptin were generally similar in healthy subjects and in patients with type 2 diabetes.

Absorption:

The absolute bioavailability of sitagliptin is approximately 87 %. Co-administration of a high fat meal with sitagliptin has no effect on the pharmacokinetics (see section 4.2).

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 isoenzymes 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.

Special Populations:

Type 2 diabetes:

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 patients with ESRD on haemodialysis. Sitagliptin was modestly removed by haemodialysis (13,5 % over a 3 to 4 hour haemodialysis session starting 4 hours post-dose). To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with GFR < 45 mL/min (see section 4.2).

Hepatic impairment:

No dose adjustment for sitagliptin 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.

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.

Paediatric population:

No studies with sitagliptin have been performed in paediatric patients.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core:

Calcium Hydrogen Phosphate Anhydrous,

Microcrystalline cellulose

Croscarmellose sodium

Low-Substituted Hydroxypropyl Cellulose,

Colloidal Silicon Dioxide

Magnesium stearate

Sodium stearyl fumarate

Film coating:

Hydroxypropylmethyl cellulose viscosity grade 6 mPa s (2 %. 20 °C)

Hydroxypropylcellulose. viscosity grade 300 – 600 mPa s (10 %. 25 °C)

Polyethylene glycol 6000

Titanium dioxide (E 171)

Ferric oxide, yellow (E 172)

Ferric oxide, red (E 172)

Ferric oxide, black (E 172) (100 mg only)

Talc

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store below 30 °C

6.5. Nature and contents of container

JOSISITIN 25 mg, 50 mg or 100 mg film coated tablets are packed in Al/Al blisters and PVDC blisters, in packs of 28, 30, 56 and 60 tablets with blisters of 7 or 10 tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

8. REGISTRATION NUMBER

To be allocated by SAHPRA upon registration

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: To be allocated by SAHPRA upon registration

10. DATE OF REVISION OF THE TEXT

Not applicable.

[1]Company Reg. No.: 1990/001979/07