

## **Summary of Product Characteristics for Pharmaceutical Products**

### **1. Name of the Medicinal Product**

SITAGOOD 50MG TABLET

### **2. Qualitative And Quantitative Composition**

Each film-coated Tablet contains Sitagliptin Phosphate Monohydrate USP Eq. to Sitagliptin 50 mg

*For the full list of excipients, see section 6.1.*

### **3. Pharmaceutical Form**

Film-coated Tablet.

A dark yellow colored round shaped biconvex film coated tablets both sides plain.

### **4. Clinical Particulars**

#### **4.1 Therapeutic indications**

For adult patients with type 2 diabetes mellitus, SITAGOOD 50 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 (PPAR $\gamma$ ) agonist (i.e. a thiazolidinedione) when use of a PPAR $\gamma$  agonist is appropriate and when diet and exercise plus the PPAR $\gamma$  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 PPAR $\gamma$  agonist and metformin when use of a PPAR $\gamma$  agonist is appropriate and when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

SITAGOOD 50 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 PPAR $\gamma$  agonist, the dose of metformin and/or PPAR $\gamma$  agonist should be maintained, and SITAGOOD 50 administered concomitantly.

When SITAGOOD 50 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 SITAGOOD 50 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]  $\geq 60$  to  $< 90$  mL/min), no dose adjustment is required.

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

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

For patients with severe renal impairment (GFR  $\geq 15$  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 SITAGOOD 50 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 SITAGOOD 50 and periodically thereafter.

##### *Hepatic impairment*

No dose adjustment is necessary for patients with mild to moderate hepatic impairment. SITAGOOD 50 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:*

SITAGOOD 50 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).

### **Special warnings and precautions for use**

#### General

Sitagliptin-50 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, Sitagliptin-50 and other potentially suspect medicinal products should be discontinued; if acute pancreatitis is confirmed, Sitagliptin-50 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 Sitagliptin-50 as monotherapy and as part of combination therapy with medicinal products not known to cause hypoglycaemia (i.e. metformin and/or a PPAR $\gamma$  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, Sitagliptin-50 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, Sitagliptin-50 should be discontinued.

#### *Sodium*

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

#### **4.4 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<sub>max</sub> 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<sub>max</sub> 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.

#### **4.5 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, Sitagliptin-50 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-50 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.

#### **4.6 Effects on ability to drive and use machines**

SITAGOOD 50 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 Sitagliptin-50 is used in combination with a sulphonylurea or with insulin.

#### **4.7 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 %).

##### Tabulated list of adverse reactions

Adverse reactions are listed below (Table 1) by system organ class and frequency. Frequencies are defined as: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  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 |
|-------------------------|-------------------------------|
| Immune system disorders |                               |

|                                                                               |                     |
|-------------------------------------------------------------------------------|---------------------|
| hypersensitivity reactions including anaphylactic responses <sup>*,†</sup>    | Frequency not known |
| <b>Metabolism and nutrition disorders</b>                                     |                     |
| hypoglycaemia <sup>†</sup>                                                    | Common              |
| <b>Nervous system disorders</b>                                               |                     |
| headache                                                                      | Common              |
| dizziness                                                                     | Uncommon            |
| <b>Respiratory, thoracic and mediastinal disorders</b>                        |                     |
| interstitial lung disease <sup>*</sup>                                        | Frequency not known |
| <b>Gastrointestinal disorders</b>                                             |                     |
| constipation                                                                  | Uncommon            |
| vomiting <sup>*</sup>                                                         | Frequency not known |
| acute pancreatitis <sup>*,†,‡</sup>                                           | Frequency not known |
| fatal and non-fatal haemorrhagic and necrotizing pancreatitis <sup>*,†</sup>  | Frequency not known |
| <b>Skin and subcutaneous tissue disorders</b>                                 |                     |
| pruritus <sup>*</sup>                                                         | Uncommon            |
| angioedema <sup>*,†</sup>                                                     | Frequency not known |
| rash <sup>*,†</sup>                                                           | Frequency not known |
| urticaria <sup>*,†</sup>                                                      | Frequency not known |
| cutaneous vasculitis <sup>*,†</sup>                                           | Frequency not known |
| exfoliative skin conditions including Stevens-Johnson syndrome <sup>*,†</sup> | Frequency not known |
| bullous pemphigoid <sup>*</sup>                                               | Frequency not known |
| <b>Musculoskeletal and connective tissue disorders</b>                        |                     |
| arthralgia <sup>*</sup>                                                       | Frequency not known |
| myalgia <sup>*</sup>                                                          | Frequency not known |
| back pain <sup>*</sup>                                                        | Frequency not known |
| arthropathy <sup>*</sup>                                                      | Frequency not known |
| <b>Renal and urinary disorders</b>                                            |                     |
| impaired renal function <sup>*</sup>                                          | Frequency not known |
| acute renal failure <sup>*</sup>                                              | Frequency not known |

\*Adverse reactions were identified through postmarketing 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)).

#### 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  $\geq 30$  and  $< 50$  mL/min/1.73 m<sup>2</sup>), and 7,339 patients treated with placebo in the intention-to-treat population. Both treatments were added to usual care targeting regional standards for HbA1c 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 sulphonylurea 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 sulphonylurea 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.

#### **4.8 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.

#### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorization 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 Pharmacy and Poisons Board- Pharmacovigilance Electronic Reporting System (PvERS);

<https://pv.pharmacyboardkenya.org> .

#### **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

SITAGOOD 50 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 insulintropic 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 A1c (HbA1c) 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.

## **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<sub>max</sub>) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8.52 µM•hr, C<sub>max</sub> 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, SITAGOOD 50 may be administered with or without food.

Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for C<sub>max</sub> and C<sub>24hr</sub> (C<sub>max</sub> increased in a greater than dose-proportional manner and C<sub>24hr</sub> 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 [<sup>14</sup>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 [<sup>14</sup>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<sub>1/2</sub> 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 (IC<sub>50</sub>=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 ( $\text{GFR} \geq 60$  to  $< 90$  mL/min) and patients with moderate renal impairment ( $\text{GFR} \geq 45$  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 ( $\text{GFR} \geq 30$  to  $< 45$  mL/min), and approximately 4-fold in patients with severe renal impairment ( $\text{GFR} < 30$  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  $\text{GFR} < 45$  mL/min.

#### *Hepatic impairment*

No dose adjustment for SITAGOOD 50 is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score  $\leq 9$ ). 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.

### **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.

## **6. Pharmaceutical Particulars**

### **6.1 List Of Excipients**

Dibasic Calcium Phosphate USP

Microcrystalline Cellulose Phosphate (Avicel-102) USP

Povidone K-30 USP

Purified Water USP

Magnesium Stearate USP

Croscarmellose Sodium USP

Dichloromethane USP

Isopropyl Alcohol USP

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

36 months from date of manufacturing.

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

10 tablets are packed in one Alu-Alu blister such 3 blisters are packed in a carton with insert.

### **6.6 Special Precautions for disposal and other handling**

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.

This medicine does not require any special storage conditions.

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.

**7. Marketing Authorization Holder**

ZAIN PHARMA LIMITED.

Plot No: 209/13741, Colchester Park,

Go-Down No.1, 2, 3, Off Mombasa Road, Behind Nice and Lovely House

P.O. Box: 100167-00101, Nairobi, Kenya

**8. Marketing Authorization Number (S)**

H2026/CTD11576/25234

**9. Date Of First Authorization/ Renewal of the Authorization**

2026 June 12

**10. Date of revision of the text**

2026 June 12