SITAVIO

Sitagliptin

1. NAME OF THE MEDICINAL PRODUCT
Sitavio 50mg Film Coated Tablets
Sitavio 100mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Sitavio 50mg Film Coated Tablets: Each tablet contains 64.250mg of Sitagliptin Phosphate Monohydrate equivalent to 50mg Sitagliptin.
Sitavio 100mg Film Coated Tablets: Each tablet contains 128.500mg of Sitagliptin Phosphate Monohydrate equivalent to 100mg Sitagliptin.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film Coated Tablets.
Sitavio 50mg Film Coated Tablets: Beige, round shaped film coated tablet debossed with 'C 33' on one side of the tablet and plain on the other side
Sitavio 100mg Film Coated Tablets: Beige, round shaped film coated tablet debossed with 'C 32' on one side of the tablet and plain on the other side

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Monotherapy
Sitavio is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

Combination with metformin
Sitavio is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin as initial therapy or when the single agent alone, with diet and exercise, does not provide adequate glycemic control. Initial combination therapy or maintenance of combination therapy may not be appropriate for all patients. These management options are left to the discretion of the health care provider.

Combination with a sulphonylurea
Sitavio is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with a sulphonylureas when treatment with maximal tolerated dose of sulphonylurea alone, with diet and exercise, does not provide adequate glycemic control and when metformin is inappropriate due to contraindications or intolerance.

Combination with metformin and a sulphonylurea
Sitavio is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin and a sulphonylurea when dual therapy with these two agents and with diet and exercise does not provide adequate glycemic control.

Combination with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist
Sitavio is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with a PPARγ agonist (i.e. thiazolidinediones) when diet and exercise, plus the single agent do not provide adequate glycemic control.

Combination with metformin and a PPARγ agonist
Sitavio is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin and a PPARγ agonist (i.e., thiazolidinediones) when dual therapy with these agents, with diet and exercise, does not provide adequate glycemic control.

Combination with Insulin
Sitavio is indicated in patients with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control in combination with insulin (with or without metformin).

4.2 Posology and method of administration
The recommended dose of Sitagliptin is 100 mg once daily as monotherapy or as combination therapy with metformin, a sulfonylurea, insulin (with or without metformin), a PPARγ agonist (i.e., thiazolidinediones), metformin plus a sulfonylurea, or metformin plus a PPARγ agonist. Sitagliptin can be taken with or without food. When Sitagliptin is used in combination with a sulfonylurea or with insulin, a lower dose of sulfonylurea or insulin may be considered to reduce the risk of sulfonylurea- or insulin-induced hypoglycaemia.

Patients with Renal Impairment
Because there is a dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of Sitagliptin and periodically thereafter.
For patients with mild renal impairment (estimated glomerular filtration rate [eGFR] ≥ 60 mL/min/1.73 m^2 to < 90 mL/min/1.73 m^2), no dosage adjustment for Sitagliptin is required.
For patients with moderate renal impairment (eGFR ≥ 45 mL/min.1.73 m^2 to < 60 mL/min.1.73 m^2), no dosage adjustment for Sitagliptin is required.
For patients with moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m^2 to 45 mL/min/1.73 m^2), the dose of Sitagliptin is 50 mg once daily.
For patients with severe renal impairment (eGFR ≥ 15 mL/min/1.73 m^2 to < 30 mL/min/1.73 m^2) or with end-stage renal disease (ESRD) (eGFR < 15 mL/min/1.73 m^2), including those 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.

Pediatric population
Sitagliptin should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy. Sitagliptin has not been studied in pediatric patients under 10 years of age.

Method of administration
For oral use. Can be taken with or without food.

4.3 Contraindications
Sitagliptin is contraindicated in patients who are hypersensitive to any components of this product.

4.4 Special warnings and precautions for use
General
Sitagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Pancreatitis: There have been reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin. 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. If pancreatitis is suspected, Sitagliptin and other potentially suspect medicinal products should be discontinued.

Use in Patients with 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 eGFR< 45 mL/min/1.73 m^2), as well as in ESRD patients requiring hemodialysis or peritoneal dialysis.

Hypoglycemia in Combination with a Sulfonylurea or with Insulin: Hypoglycemia has been observed when Sitagliptin was used in combination with insulin or a sulfonylurea. Therefore, to reduce the risk of sulfonylurea- or insulin-induced hypoglycemia, a lower dose of sulfonylurea or insulin may be considered.

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. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. 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.

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 DPP-4 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.

4.5 Interaction with other medicinal products and other forms of interaction
Sitagliptin did not have clinically meaningful effects on the pharmacokinetics of the following: metformin, rosiglitazone, glyburide, simvastatin, warfarin, and oral contraceptives. Based on these data, sitagliptin does not inhibit CYP isozymes CYP3A4, 2C8, or 2C9. Based on *in vitro* data, sitagliptin is also not expected to inhibit CYP2D6, 1A2, 2C19 or 2B6 or to induce CYP3A4.
Co-administration of multiple twice-daily doses of metformin with sitagliptin did not meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.
Population pharmacokinetic analyses have been conducted in patients with type 2 diabetes. Concomitant medications did not have a clinically meaningful effect on the pharmacokinetics of sitagliptin. Medications assessed were those that are commonly administered to patients with type 2 diabetes including cholesterol-lowering agents (e.g., statins, fibrates, ezetimibe), anti-platelet agents (e.g., clopidogrel), antihypertensives (e.g., ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, hydrochlorothiazide), analgesics and non-steroidal anti-inflammatory agents (e.g., naproxen, diclofenac, celecoxib), anti-depressants (e.g., bupropion, fluoxetine, sertraline), antihistamines (e.g., cetirizine), proton-pump inhibitors (e.g., omeprazole, lansoprazole), and medications for erectile dysfunction (e.g., sildenafil).
There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (C_{max}, 18%) of digoxin with the co-administration of sitagliptin. These increases are not considered to be clinically meaningful. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or Sitagliptin is recommended.
The AUC and C_{max} of sitagliptin were increased approximately 29% and 68%, respectively, in subjects with co-administration of a single 100-mg oral dose of Sitagliptin and a single 600-mg oral dose of cyclosporine, a potent probe inhibitor of p-glycoprotein. The observed changes in sitagliptin pharmacokinetics are not considered to be clinically meaningful. No dosage adjustment for Sitagliptin is recommended when co-administered with cyclosporine or other p- glycoprotein inhibitors (e.g., ketoconazole).

4.6 Fertility, pregnancy and lactation
Pregnancy
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. Sitagliptin should not be used during breast-feeding.

Fertility
Human data are lacking.

4.7 Effects on ability to drive and use machines
Sitagliptin 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 is used in combination with a sulphonylurea or with insulin.

4.8 Undesirable effects
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 %).

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 section Special warnings and precautions for use.
‡ 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
The profile of adverse reactions in paediatric patients with type 2 diabetes mellitus aged 10 to 17 years 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 m2), 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 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.

4.9 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 if required.
Sitagliptin is modestly dialyzable. 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 member of a class of oral anti-hyperglycemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors, which improve glycemic control in patients with type 2 diabetes 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 hypoglycemia. 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 hyperglycemia, these changes in insulin and glucagon levels lead

to lower hemoglobin A1c (HbA1c) and lower fasting and post-prandial glucose concentrations. The glucose-dependent mechanism of sitagliptin is distinct from the mechanism of sulfonylureas, which increase insulin secretion even when glucose levels are low and can lead to hypoglycemia 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.

5.2 Pharmacokinetic properties
Absorption
The absolute bioavailability of sitagliptin is approximately 87%. Since co-administration of a high-fat meal with Sitagliptin had no effect on the pharmacokinetics, Sitagliptin may be administered with or without food.

Distribution
The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 liters. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).

Metabolism
Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79% of sitagliptin is excreted unchanged in the urine.
Following a [^{14}C] sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

Elimination
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. 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.
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.

Characteristics in patients
Type 2 Diabetes
The pharmacokinetics of sitagliptin in patients with type 2 diabetes are generally similar to those in healthy subjects.

Renal Impairment
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 (eGFR ≥ 60 mL/min/1.73 m^2 to < 90 mL/min/1.73 m^2) and patients with moderate renal impairment (eGFR ≥ 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2), 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 (eGFR ≥ 30 mL/min/1.73 m^2 to < 45 mL/min/1.73 m^2), and approximately 4-fold in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), including patients with ESRD on hemodialysis. Sitagliptin was modestly removed by hemodialysis (13.5% over a 3- to 4-hour hemodialysis 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 eGFR <45 mL/min/1.73 m^2.

Hepatic Impairment
In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and C_{max} of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100-mg dose of Sitagliptin. These differences are not considered to be clinically meaningful. No dosage adjustment for Sitagliptin is necessary for patients with mild or moderate hepatic impairment.
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 dosage adjustment is required based on age. Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

Pediatric
The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in pediatric 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 based on the flat PK/PD relationship between the dose of 50 mg and 100 mg in adults.
No studies with sitagliptin have been performed in pediatric patients < 10 years of age.

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.

6. PHARMACOLOGICAL PROPERTIES
6.1 List of excipients
Tablet core:
Microcrystalline Cellulose, Anhydrous Dibasic Calcium Phosphate, Croscarmellose Sodium, Sodium Stearyl Fumarate, Magnesium Stearate

Film-coat:
Opadry II Complete Film Coating System 85F17438 Beige

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Please refer to the expiry date on the product labels.

6.4 Special precautions for storage
Store below 30°C.

6.5. Nature and contents of containers
Alu/PVC/PE/PVDC White Opaque blisters of 1 x 10's, 3 x 10's, 6 x 10's, 10 x 10's, 50 x 10's, 100 x 10's in blister form packed in the outer carton. Not all pack sizes may be marketed.

6.6. Special precautions for disposal
No special requirement.

7. MANUFACTURER
Manufactured by:
Novugen Pharma Sdn. Bhd.
No. 27, Jalan Lengkuk Teknologi 2,
Taman Teknologi Enstek Fasa 1,
71760 Bandar Baru Enstek,
Negeri Sembilan, Malaysia

Product Registration Holder:
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Shah Alam, Selangor, Malaysia

8. DATE OF REVISION
15/03/2023