Important information. Please read carefully.

STAGEO Film-Coated Tablets 100mg

COMPOSITION
Each film coated tablet contains Sitagliptin Phosphate Monohydrate, equivalent to 100mg Sitagliptin.

PHARMACODYNAMICS
Mechanism of action

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 postprandial 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.
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.

PHARMACOKINETICS
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 post-dose, mean plasma AUC of Sitagliptin was 8.52 μM•hr, Cmax 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, Sitagliptin may be administered with or without food.
Plasma AUC of Sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for Cmax and C24hr.

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%).

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. 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, approximately 100% of the administered radioactivity was eliminated in faeces (13%) or urine (87%) within one week of dosing. The apparent terminal t½ following a 100mg oral dose of Sitagliptin was approximately 12.4 hours and renal clearance was approximately 350mL/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. 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:

Compared to normal healthy subjects, plasma AUC of Sitagliptin has been reported to increase 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 has been reported to increase approximately 2-fold in patients with moderate renal impairment (GFR ≥ 30 < 45 ml/min), and approximately 4-fold in patients with severe renal impairment (GFR < 30 ml/min), including patients with ESRD on haemodialysis. Sitagliptin has been reported to be 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.

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 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. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of Sitagliptin compared to younger subjects.

Pediatric:

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.

INDICATIONS

Monotherapy

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

Combination with metformin
Sitagliptin 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
Sitagliptin 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
Sitagliptin 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
Sitagliptin 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
Sitagliptin 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
Sitagliptin 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).

DOSAGE AND ADMINISTRATION
For oral 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.

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 [GFR] ≥60 to < 90 ml/min), no dosage adjustment for Sitagliptin is required.
For patients with moderate renal impairment (GFR ≥ 45 to < 60 ml/min), no dosage adjustment for Sitagliptin is required.
For patients with moderate renal impairment (GFR ≥ 30 to 45 ml/min), the dose of Sitagliptin is 50 mg once daily.
For patients with severe renal impairment (GFR ≥ 15 to 30 ml/min) or with end-stage renal disease (ESRD) (GFR < 15 mL/min), including those requiring hemodialysis or peritoneal dialysis, the dose of Sitagliptin is 25 mg once daily. Sitagliptin may be administered without regard to the timing of dialysis.

The dose adjustment is based upon renal function, assessment of renal function is recommended prior to initiation of Sitagliptin and periodically thereafter.

Hepatic Impairment
No dose adjustment is necessary for patients with mild to moderate hepatic impairment. Sitagliptin has not been studied in patients with severe hepatic impairment and care should be exercised. Nevertheless,

Sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetic of Sitagliptin.

Elderly
No dose adjustment is necessary based on age.

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.

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

WARNINGS AND PRECAUTIONS
General
Sitagliptin 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 and other potentially suspect medicinal products should be discontinued; if acute pancreatitis is confirmed, Sitagliptin should not be restarted.
Caution should be exercised in patients with a history of pancreatitis.

Hypoglycaemia when used in combination with other anti-hypoglycemia medical products
Hypoglycaemia has been observed when Sitagliptin was used in combination with insulin or a sulphonyurea. Therefore, to reduce the risk of hypoglycaemia, a lower dose sulphonylurea or insulin may be considered.

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 hemodialysis or peritoneal dialysis.
When considering the use of Sitagliptin in combination with another antidiabetic medicinal product, its conditions for use in patients with renal impairment should be checked.

Hypersensitivity Reactions:
Hypersensitivity reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. If a hypersensitivity reaction is suspected, discontinue Sitagliptin, assess for other potential causes for the event, and institute alternative treatment for diabetes.

Bullous Pemphigoid:
Post-marketing reports of bullous pemphigoid in patients taking DPP4 inhibitors including Sitagliptin. If bullous pemphigoid is suspected, Sitagliptin should be discontinued.

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

DRUG INTERACTIONS
Effects of Other Medicinal Product on Sitagliptin
Primary enzyme responsible for limited metabolism of Sitagliptin is CYP3A4, with contribution from CYP2C8. In patient 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 elimination of Sitagliptin in the setting of severe renal impairment or end-stage renal disease (ESRD). Therefore, it is possible that potent CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the pharmacokinetics of Sitagliptin in patient with severe renal impairment or ESRD.

Sitagliptin is 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 clinical meaningful interaction is considered to be low. Concomitant administration of OAT3 inhibitors has not been evaluate in vivo.

Ciclosporin: Meaningful interactions would not be expected with p-glycoprotein inhibitors.

Effects of Sitagliptin on Other Medicinal Products
Digoxin: Sitagliptin had a small effect on plasma digoxin concentrations. 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.

Sitagliptin does not inhibit nor induce CYP450 isoenzymes. Sitagliptin did not meaningfully alter the pharmacokinetics of 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 (OTC). Sitagliptin may be a mild inhibitor of p-glycoprotein in vivo.

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 human is unknown. Due to lack of human data, Sitagliptin should not be used during pregnancy.

Nursing Mothers
It is not known whether Sitagliptin is secreted in human breast milk. Animal studies have shown excretion of Sitagliptin in breast milk. Therefore, 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.

SIDE EFFECTS
Serious adverse reactions including pancreatitis and hypersensitivity reactions have been reported. Hypoglycemia has been reported in combination with Sulphonylurea and insulin.

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

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	
hypoglycemia	Common
Nervous System Disorders	
headache	common
dizziness	uncommon
Respiratory, thoracic and mediastinal disorders	
Intersitial 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 tissues 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 pamphigoid	frequency not known
Muscoloskeletal and connective tissues disorders	
arthralgia	frequency not known
myalgia	frequency not known
backpain	frequency not known
arthopathy	frequency not known
Renal and urinary disorders	
impaired renal function	frequency not known
acute renal failure	frequency not known

SYMPTOMS AND TREATMENT FOR OVERDOSAGE
Single doses of up to 800 mg Sitagliptin were generally well tolerated. Minimal increases in QTc, not considered to be clinically relevant. There is no experience with doses above 800 mg. 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 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.

STORAGE CONDITION
Store below 30°C.

SHELF LIFE
The expiry date is indicated on the packaging.

PRODUCT DESCRIPTION, DOSAGE FORM AND PACKAGING AVAILABLE
Beige, round, normal convex, heart logo on upper side and plain on lower side, 10.0 mm in diameter
Available in pack sizes of 3x10 tablets.

For further information, please consult your physician or pharmacist. Revision Date: 29/01/2026

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