MedChoice™
Endocrine

℞

Sitagliptin
Gliptadin

50 mg ● **100** mg Film-Coated Tablet
DIPEPTIDYL PEPTIDASE 4
(DPP-4) INHIBITOR

Formulation:
Each film-coated tablet contains:
64.25 mg of Sitagliptin Phosphate Monohydrate USP
eq. to Sitagliptin ..... 50 mg

Each film-coated tablet contains:
128.50 mg of Sitagliptin Phosphate Monohydrate USP
eq. to Sitagliptin ..... 100 mg

Product Description:
Gliptadin 50 mg: White to off white colored circular, biconvex, film-coated tablets scored on one side and plain on other side.

Gliptadin 100 mg: Blue colored, film-coated tablets scored on one side and plain on other side.

Pharmacological Properties:
Pharmacodynamic Properties
Mechanism of action
Sitagliptin is a member of a class of oral anti-hyperglycemic agents called dipeptidyl peptidase-4 (DPP-4) inhibitors. The improvement in glycemic 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 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 sulfonylurea, 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.
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.

Pharmacokinetic Properties
Absorption
Following 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 (Cmax increased in a greater than dose-proportional manner and C24hr 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 L. 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 [14C]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 [14C]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 t1/2 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, cyclosporin, 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.

Indications:
For adult patients with type 2 diabetes mellitus, sitagliptin tablets is indicated to improve glycemic 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 glycemic control.
• a sulfonylurea when diet and exercise plus maximal tolerated dose of a sulfonylurea alone do not provide adequate glycemic control and when metformin is inappropriate due to contraindications or intolerance.
• a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e. a thiazolidinedione) when use of a PPARγ agonist is appropriate and when diet and exercise plus the PPARγ agonist alone do not provide adequate glycemic control.
As triple oral therapy in combination with
• a sulfonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycemic control.
• a PPARγ agonist and metformin when use of a PPARγ agonist is appropriate and when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycemic control.
Sitagliptin tablet 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 glycemic control.

Dosage and Administration:
Dosage:
The dose is 100 mg sitagliptin once daily. When used in combination with metformin and/or a PPARγ agonist, the dose of metformin and/or PPARγ agonist should be maintained, and sitagliptin tablets administered concomitantly.
When sitagliptin tablet is used in combination with a sulfonylurea or with insulin, a lower dose of the sulfonylurea or insulin may be considered to reduce the risk of hypoglycemia.
If a dose of sitagliptin tablet 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 (creatinine clearance [CrCl] $\geq$ 50 mL/min), no dose adjustment is required.
For patients with moderate renal impairment (CrCl $\leq$ 30 to < 50 mL/min), the dose of sitagliptin tablets is 50 mg once daily.
For patients with severe renal impairment (CrCl <30 mL/min) or with end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis, the dose of sitagliptin tablet 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 sitagliptin tablets and periodically thereafter.
Hepatic impairment
No dose adjustment is necessary for patients with mild to moderate hepatic impairment. Sitagliptin tablets has not been studied in patients with severe hepatic impairment and care should be exercised.
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.

Pediatric population
The safety and efficacy of sitagliptin in children and adolescents under 18 years of age have not yet been established. No data are available.

Method of administration:
Sitagliptin can be taken orally with or without food.

Contraindications:
Hypersensitivity to the active substance or to any of the excipients.

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 necrotizing or hemorrhagic 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.
Hypoglycemia when used in combination with other anti-hyperglycemic medicinal products
In clinical trials of sitagliptin as monotherapy and as part of combination therapy with medicinal products not known to cause hypoglycemia (i.e. metformin and/or a PPARγ agonist), rates of hypoglycemia reported with sitagliptin were similar to rates in patients taking placebo. Hypoglycemia has been observed when sitagliptin was used in combination with insulin or a sulfonylurea. Therefore, to reduce the risk of hypoglycemia, a lower dose of sulfonylurea 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 moderate and severe renal impairment, as well as in ESRD patients requiring hemodialysis or peritoneal dialysis.

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 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 should be discontinued.

Drug Interactions:

Effects of other medicinal products on sitagliptin

Clinical data described below suggest that the risk for clinically meaningful interactions by co-administered medicinal products is low.

In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin is CYP3A4, with contribution from CYP2C8. In patients with normal renal function, metabolism, including via CYP3A4, plays only a small role in the clearance of sitagliptin. Metabolism may play a more significant role in the elimination of sitagliptin in the setting of severe renal impairment or end-stage renal disease (ESRD). For this reason, it is possible that potent CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the phamacokinetics of sitagliptin in patients with severe renal impairment or ESRD. The 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.

Cyclosporin: A study was conducted to assess the effect of cyclosporin, 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 cyclosporin increased the AUC and Cmax 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 Cmax 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.

Ofloxacin: Ofloxacin enhances effects of sitagliptin by pharmacodynamic synergism. Quinolone antibiotic administration with sitagliptin may resultin hyperglycemia or hypoglycemia causing somnolence, dizziness and visual disturbances, hence, caution should be exercised when driving or operating machinery.

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, sitagliptin 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. Sitagliptin should not be used during breastfeeding.

Fertility

Animal data do not suggest an effect of treatment with sitagliptin on male and female fertility. Human data are lacking.

Effects on Ability to Drive and Use Machines

There have been occasional reports of somnolence, impairment of skills, dizziness and visual disturbances with sitagliptin, therefore, caution should be exercised when driving or operating machinery. This effects maybe enhanced by alcohol.

Adverse Drug Reactions:

Serious adverse reactions including pancreatitis and hypersensitivity reactions have been reported. Hypoglycemia has been reported in combination with sulfonylurea (4.7%-13.8%) and insulin (9.6%).

Tabulated list of adverse reactions are listed below (Table 1) by system organ class and frequency.

Frequencies are defined as: very common (≥1/10); common (≥1/100 to < 1/10); uncommon (≥1/1,000 to < 1/100); rare (≥1/10,000 to < 1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data).

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

Adverse reaction	Frequency of adverse reaction
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	
interstitial lung disease*	Frequency not known
Gastrointestinal disorders	
constipation	Uncommon
vomiting*	Frequency not known
acute pancreatitis*,†,‡	Frequency not known
fatal and non-fatal hemorrhagic 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

Overdose and Treatment:

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 hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.

Caution:

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

"For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph. Seek medical attention immediately at the first sign of any adverse drug reaction."

Storage Condition:

Store at temperatures not exceeding 30°C.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

Availability:

Alu/Alu Blister Pack x 10's (Box of 30's)

Gliptadin 50
DRP-8901-02
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Date of Last Revision of Package Insert: March 16, 2022

Gliptadin 100
DRP-8900-02
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Gliptadin 50
UNDER DRUG PRICE REGULATION
RETAIL PRICE NOT TO EXCEED Php 53.19

Gliptadin 100
UNDER DRUG PRICE REGULATION
RETAIL PRICE NOT TO EXCEED Php 65.37

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