SITAGLIPTIN

25 mg Film-Coated Tablet
50 mg Film-Coated Tablet
100 mg Film-Coated Tablet
Dipeptidyl Peptidase 4 (DDP-4) Inhibitor

FORMULATION:
Each Film-Coated Tablet contains:
Sitagliptin (as phosphate monohydrate), USP..... 32.12 mg equivalent to 25 mg
Sitagliptin (as phosphate monohydrate), USP..... 64.24 mg equivalent to 50 mg
Sitagliptin (as phosphate monohydrate), USP..... 128.5 mg equivalent to 100 mg

PRODUCT DESCRIPTION:
Sitagliptin 25 mg Film-Coated Tablet is available as peach to light orange, circular, biconvex film-coated tablet, plain on both sides packed in Alu/Alu Blister Pack x 10's (Box of 30's).

Sitagliptin 50 mg Film-Coated Tablet is available as light beige to beige, circular, biconvex film-coated tablet, with "50" embossed on one side and with break line on the other side packed in Alu/Alu Blister Pack x 10's (Box of 30's).

Sitagliptin 100 mg Film-Coated Tablet is available as light beige to beige, circular, biconvex film-coated tablet, with "100" embossed on one side and with break line on the other side packed in Alu/Alu Blister Pack x 10's (Box of 30's).

PHARMACOKINETICS:
The pharmacokinetics of sitagliptin have been extensively characterized in healthy subjects and patients with type 2 diabetes. After oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose. Plasma AUC of sitagliptin increased in a dose-proportional manner. Following a single oral 100-mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 μM•hr, C_{max} was 950 nM, and apparent terminal half-life ($t_{1/2}$) was 12.4 hours. Plasma AUC of sitagliptin increased approximately 14% following 100-mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of sitagliptin were generally similar in healthy subjects and in patients with type 2 diabetes.

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

Distribution:
The mean volume distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subject 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
Renal Impairment: A single-dose, open-label study was conducted to evaluate the pharmacokinetics of SITAGLIPTIN PHOSPHATE (100 mg dose) 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 hemodialysis. 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 (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 PHOSPHATE. These differences are not considered to be clinically meaningful. No dosage adjustment for SITAGLIPTIN PHOSPHATE 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: No studies with SITAGLIPTIN PHOSPHATE have been performed in pediatric patients.

Gender: No dosage adjustment is necessary based on gender. Gender had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

Race: No dosage adjustment is necessary based on race. Race had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data, including subjects of white, Hispanic, black, Asian, and other racial groups.

Body Mass Index (BMI): No dosage adjustment is necessary based on BMI. Body mass index had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

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

PHARMACODYNAMICS
General:
In patients with type 2 diabetes, administration of single oral doses of SITAGLIPTIN PHOSPHATE leads to inhibition of DPP-4 enzyme activity for a 24-hour period, resulting in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, increased plasma levels of insulin and C-peptide, decreased glucagon concentrations, reduced fasting glucose, and reduced glucose excursion following an oral glucose load or a meal.

INDICATIONS:
Monotherapy
SITAGLIPTIN PHOSPHATE is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

Combination with Metformin
SITAGLIPTIN PHOSPHATE 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.

Combination with a Sulfonylurea
SITAGLIPTIN PHOSPHATE is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with a sulfonylurea when treatment with the single agent alone, with diet and exercise, does not provide adequate glycemic control.

Combination with a PPARγ agonist
SITAGLIPTIN PHOSPHATE is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with a PPARγ agonist (i.e., thiazolidinediones) as initial therapy or when the single agent alone, with diet and exercise, does not provide adequate glycemic control.

Combination with Metformin and a Sulfonylurea
SITAGLIPTIN PHOSPHATE is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin and a sulfonylurea when dual therapy with these agents, with diet and exercise, does not provide adequate glycemic control.

Combination with Metformin and a PPARγ agonist
SITAGLIPTIN PHOSPHATE 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 PHOSPHATE 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:
The recommended dose of SITAGLIPTIN PHOSPHATE is 100 mg once daily as monotherapy or as combination

therapy with metformin, a sulfonylurea, insulin (with or without metformin), a PPARγ agonist (e.g., thiazolidinediones), metformin plus a sulfonylurea, or metformin plus a PPARγ agonist.

When SITAGLIPTIN PHOSPHATE 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 hypoglycemia.

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 PHOSPHATE 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 PHOSPHATE 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 PHOSPHATE 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 PHOSPHATE 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 PHOSPHATE is 25 mg once daily. SITAGLIPTIN PHOSPHATE may be administered without regard to the timing of dialysis.

MODE OF ADMINISTRATION:
SITAGLIPTIN PHOSPHATE can be taken orally with or without food.

CONTRAINDICATIONS:
SITAGLIPTIN PHOSPHATE is contraindicated in patients who are hypersensitive to any components of this product.

WARNINGS AND PRECAUTIONS:
General
SITAGLIPTIN PHOSPHATE 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 PHOSPHATE and other potentially suspect medicinal products should be discontinued.

Use in Patients with Renal Impairment: SITAGLIPTIN PHOSPHATE is renally excreted. To achieve plasma concentrations of SITAGLIPTIN PHOSPHATE 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: In clinical trials of SITAGLIPTIN PHOSPHATE as monotherapy and as part of combination therapy with agents not known to cause hypoglycemia (i.e. metformin or a PPARγ agonist (thiazolidinedione), rates of hypoglycemia reported with SITAGLIPTIN PHOSPHATE were similar to rates in patients taking placebo. As is typical with other antihyperglycemic agents, hypoglycemia has been observed when SITAGLIPTIN PHOSPHATE 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 PHOSPHATE. 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 PHOSPHATE, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue SITAGLIPTIN PHOSPHATE, assess for other potential causes for the event, and institute alternative treatment for diabetes.

Use in Children: Safety and effectiveness of SITAGLIPTIN PHOSPHATE in pediatric patients under 18 years have not been established.

Use in Elderly: In clinical studies, the safety and effectiveness of SITAGLIPTIN PHOSPHATE in the elderly (≥65 years) were comparable to those seen in younger patients (<65 years). No dosage adjustment is required based on age. Elderly patients are more likely to have renal impairment; as with other patients, dosage adjustment may be required in the presence of significant renal impairment.

DRUG INTERACTIONS:
In drug interaction studies, 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 chlolesterol-lowering agents (e.g., statins, fibrates, ezetimibe), anti-platelet agents (e.g., clopidogrel), antihypersentives (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., omeprazole, lanzoprazole), and medications for erectile dysfunction (e.g., sildenafil).

There was a slight increase in the area under the curve (AUC, 11%) and 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 approximately. No dosage adjustment of digoxin or SITAGLIPTIN PHOSPHATE 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 PHOSPHATE and a single 600-mg oral dose of cyclosporine are not considered to be clinically meaningful. No dosage adjustment for SITAGLIPTIN PHOSPHATE is recommended when co-administered with cyclosporine or other p-glycoprotein inhibitors (e.g., ketoconazole).

PREGNANCY AND LACTATION:
Sitagliptin was not teratogenic in rats at oral doses up to 250mg/kg or in rabbits given up to 125mg/kg during organogenesis (up to 32 and 22 times, respectively, the human exposure based on the recommended daily adult dose of 100mg/day). In rats, a slight increase in the incidence of fetal rib malformations (absent, hypoplastic and wavy ribs) was observed at oral doses of 1000 mg/kg/day (approximately 100 times the human exposure based on the recommended daily adult human dose of 100 mg/day). Slight decreases in mean preweaning body weights of both sexes and postweaning body weight gains of males were observed in the offspring of rats given dose of 1000 mg/kg/day. However, animal reproduction studies are not always predictive of the human response.

There are no adequate and well-controlled studies in pregnant women; therefore, the safety of SITAGLIPTIN PHOSPHATE in pregnant women is not known. SITAGLIPTIN PHOSPHATE, like other oral antihyperglycemic agents, is not recommended for use in pregnancy.

Sitagliptin is secreted in the milk of lactating rats. It is known whether sitagliptin is secreted in human milk. Therefore, SITAGLIPTIN PHOSPHATE should not be used by a woman who is nursing.

PEDIATRIC USE:
Safety and effectiveness of SITAGLIPTIN PHOSPHATE in pediatric patients under 18 years have not been established.

USE IN ELDERLY:
In clinical studies, the safety and effectiveness of SITAGLIPTIN PHOSPHATE in the elderly (≥65 years) were comparable to those seen in younger patients (<65 years). No dosage adjustment is required based on age. Elderly patients are more likely to have renal impairment; as with other patients, dosage adjustment may be required in the presence of significant renal impairment.

UNDESIRABLE EFFECTS:
SITAGLIPTIN PHOSPHATE was generally well tolerated in controlled studies as both monotherapy and combination therapy, with discontinuation of therapy due to clinical adverse experiences similar to placebo.

In four placebo-controlled clinical studies as both monotherapy (one study of 18- and one of 24-week duration) and add-on combination therapy with metformin or piglitazone (both of 24-week duration), there were 1082 patients treated with SITAGLIPTIN PHOSPHATE 100 mg once daily and 778 patients given placebo. (Two of these studies also included 456 patients treated with SITAGLIPTIN PHOSPHATE 200 mg daily, two times the recommended daily dose). There were no-drug related adverse reactions reported that occurred with an incidence of ≥1% in patients receiving SITAGLIPTIN PHOSPHATE 100 mg. Overall, the safety profile of the 200-mg daily dose was similar to that of the 100-mg daily dose.

In a prespecified pooled analysis of the above studies, the overall incidence of adverse experience of hypoglycemia in patients treated with SITAGLIPTIN PHOSPHATE 100 mg was similar to placebo (1.2% vs. 0.97%). The incidences of selected gastrointestinal adverse experiences in patients treated with SITAGLIPTIN PHOSPHATE) or placebo were: abdominal pain [SITAGLIPTIN PHOSPHATE, 2.3%; PLACEBO, 2.1%], nausea (1.4%, 0.6%), vomiting (0.8%, 0.97%), and diarrhea (3.0%, 2.3%).

In all studies, adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required.

Add-on Combination with a Sulfonylurea: In a 24-week placebo-controlled study of SITAGLIPTIN PHOSPHATE 100mg in combination with glimiperide or with glimipiride and metformin (SITAGLIPTIN PHOSPHATE, N=222; placebo, N=219), the drug related adverse reactions reported in ≥1% of patients treated with SITAGLIPTIN PHOSPHATE and more commonly than in patients treated with placebo was hypoglycemia (SITAGLIPTIN PHOSPHATE), 9.5%; placebo, 0.9%).

Add-on Combination with Metformin and a PPARγ Agonist: In a placebo-controlled study of SITAGLIPTIN PHOSPHATE 100 mg in combination with metformin and rosiglitazone (SITAGLIPTIN PHOSPHATE, N=170;

placebo, N=92), the drug-related adverse reactions reported through the primary time point at Week 10 in ≥1% of patients treated with SITAGLIPTIN PHOSPHATE and more commonly than in patients treated with placebo were: headache (SITAGLIPTIN PHOSPHATE 2.4%; placebo, 0.0%), diarrhea (1.8%, 1.1%), nausea (1.2%, 1.1%), hypoglycemia (1.2%, 0.0%), and vomiting (1.2%, 0.0%). Through Week 54, the drug-related adverse reactions reported in ≥1% of patients treated with SITAGLIPTIN PHOSPHATE and more commonly than in patients treated with placebo were: headache (2.4%, 0.0%), hypoglycemia (2.4%, 0.0%), upper respiratory tract infection (1.8%, 0.0%), nausea (1.2%, 1.1%), cough (1.2%, 0.0%), fungal skin infection (1.2%, 0.0%), peripheral edema (1.2%, 0.0%), and vomiting (1.2%, 0.0%).

Initial Combination Therapy with Metformin: In a 24-week placebo-controlled factorial study of initial therapy with sitagliptin 100 mg in combination with metformin at 1000 mg or 2000 mg per day (administered as sitagliptin 50mg/metformin 500 mg or 1000 mg twice daily), the drug-related adverse reactions reported in ≥1% of patients treated with sitagliptin plus metformin (N=372) and more commonly than in patients treated with metformin alone (N=364) were: diarrhea (sitagliptin plus metformin, 3.5%; metformin, 3.3%), dyspepsia (1.3%, 1.1%), flatulence (1.3%; 0.5%), vomiting (1.1%; 0.3%), and headache (1.3%; 1.1%). The incidence of hypoglycemia was 1.1% was 1.1% in patients given sitagliptin in combination with metformin and 0.5% in patients given metformin alone.

Initial Combination Therapy with PPARγ Agonist: In a 24-week study of initial therapy with SITAGLIPTIN PHOSPHATE at 100 mg/day in combination with pioglitazone at 30mg/day, the only drug-related adverse reaction in ≥1% of patients treated with SITAGLIPTIN PHOSPHATE with pioglitazone (N=261) and more commonly than in patients with pioglitazone alone (N=259) was (asymptomatic) decreased blood glucose (SITAGLIPTIN PHOSPHATE) with pioglitazone 1.1%; pioglitazone, 0.0%). The incidence of (asymptomatic) hypoglycemia was 0.4% in patients given SITAGLIPTIN PHOSPHATE in combination with pioglitazone and 0.8% in patients given pioglitazone.

Add-on Combination with Insulin: In a 24-week placebo-controlled study Of SITAGLIPTIN PHOSPHATE 100 mg in combination with stable-dose insulin (with or without metformin), the drug-related adverse reactions reported in ≥1% of patients treated with SITAGLIPTIN PHOSPHATE (N=322) and more commonly than in patients treated with placebo (N=319) were: hypoglycemia [SITAGLIPTIN PHOSPHATE, 9.6%; placebo, 5.3%], influenza (1.2%, 0.3%), and headache (1.2%, 0.0%). In another 24-week study of patients receiving SITAGLIPTIN PHOSPHATE as add-on therapy while undergoing insulin intensification (with or without metformin) there were no drug –related adverse reactions reported that occurred with an incidence of ≥1% in patients treated with SITAGLIPTIN PHOSPHATE 100 mg and more commonly than in patients treated with placebo.

Pancreatitis: In a pooled analysis of 19 double-blind clinical trials data from 10,426 patients randomized to receive sitagliptin 100mg/day (N=5429) or corresponding (active or placebo) control (N=4817), the incidence of acute pancreatitis was 0.1 per 100 patient-years in each group (4 patients with an event in 4708 patient-years for sitagliptin and 4 patients with an event in 3942 patient-years for control).

No clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed in patients treated with SITAGLIPTIN PHOSPHATE.

Postmarketing Experience:
Additional adverse reactions have been identified during postmarketing use of SITAGLIPTIN PHOSPHATE as monotherapy and/or in combination with other antihyperglycemic agents. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish as causal relationship to drug exposure.

Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaris, cutaneous vasculitis and exfoliative skin conditions, including Stevens-Johnson syndrome: acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis worsening renal function, including acute renal failure (sometimes requiring dialysis); upper respiratory tract infection; nasopharyngitis; constipation; vomiting; headache; arthralgia; myalgia; pain in extremity; back pain.

Laboratory Test Findings:
The incidence of laboratory adverse reactions experiences was similar in patients treated with SITAGLIPTIN PHOSPHATE 100 mg compared to patients treated with placebo. Across clinical studies, a small increase in white blood cell count (approximately 200 cells/microL difference in WBC vs placebo; mean baseline WBC approximately 6600 cells/microL) was observed due to an increase in neutrophils. This observation was seen in most but not all

OVERDOSAGE:
During controlled clinical trials in healthy subjects, single doses of up to 800 mg SITAGLIPTIN PHOSPHATE were generally well tolerated. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800mg SITAGLIPTIN PHOSPHATE. 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 PHOSPHATE with doses of up to 600mg 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., removes unabsorbed material from the gastrointestinal tract, employ clinical monitoring (Including obtaining an electrodiogram), and institute supportive therapy if required.

Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dose was removed over a 3- and 4-hour hemodialysis session. Prolonged hemodialysis may considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

STORAGE CONDITION:

Store at temperatures not exceeding 30°C

PACKAGING AVAILABILITY:
Sitagliptin (as phosphate) 25 mg Film-Coated Tablet: Alu/Alu Blister Pack x 10's (Box of 30's)
Sitagliptin (as phosphate) 50 mg Film-Coated Tablet: Alu/Alu Blister Pack x 10's (Box of 30's)
Sitagliptin (as phosphate) 100 mg Film-Coated Tablet: Alu/Alu Blister Pack x 10's (Box of 30's)

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

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

REGISTRATION NUMBER:
DRP-11198

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