Not to be sold by Retail without the prescription of a Registered Medical Practitioner

Rx

Sitagliptin Phosphate Tablets IP 100 mg

OMNISITA™-100

1. Generic name
Sitagliptin Phosphate Tablets IP 100 mg

2. Qualitative and quantitative composition
Sitagliptin Phosphate Tablets IP 100 mg
Each film coated tablet contains:
Sitagliptin Phosphate Monohydrate IP
Equivalent to Sitagliptin 100 mg
Colours: Ferric Oxide Yellow USP-NF, Ferric Oxide Red USP-NF and Titanium Dioxide IP

3. Dosage form and strength
Oral dosage form (Tablets)
Sitagliptin 100 mg

4. Clinical particulars
4.1 Therapeutic indication
It is indicated as adjunct to diet and exercise to improve glycemic control in patients with type-II diabetes.
In combination with Metformin and a PPARγ agonist, it is indicated as an adjunct to diet & exercise in adult patients with type-2 Diabetes mellitus who are inadequately controlled on combination therapy with Metformin and a PPARγ agonist.
It is indicated in combination with insulin, alone or in combination with Metformin.

Limitations of Use
Sitagliptin not to be used in type 1 diabetes.
Has not been studied in patients with a history of pancreatitis.
It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Sitagliptin.

4.2 Posology and method of administration
Recommended Dosing
The recommended dose of Sitagliptin is 100 mg once daily. Sitagliptin can be taken with or without food. Sitagliptin should be swallowed whole. The tablets must not be split, crushed, or chewed before swallowing.

Recommendations for Use in Renal Impairment
For patients with an estimated glomerular filtration rate [eGFR] greater than or equal to 45 mL/min/1.73 m2 to less than 90 mL/min/1.73 m2, no dosage adjustment for Sitagliptin is required. For patients with moderate renal impairment (eGFR greater than or equal to 30 mL/min/1.73 m2 to less than 45 mL/min/1.73 m2), the dose of Sitagliptin is 50 mg once daily. For patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m2) or with end-stage renal disease (ESRD) 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. Because there is a need for dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of Sitagliptin and periodically thereafter. There have been postmarketing reports of worsening renal function in patients with renal impairment, some of whom were prescribed inappropriate doses of Sitagliptin.

4.3 Contraindications
History of a serious hypersensitivity reaction to Sitagliptin, such as anaphylaxis or angioedema.

4.4 Special warnings and precautions for use
Pancreatitis
There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotizing pancreatitis, in patients taking Sitagliptin. After initiation of Sitagliptin, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, Sitagliptin should promptly be discontinued, and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Sitagliptin.

Heart Failure
An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class.

These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. Consider the risks and benefits of Sitagliptin prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of Sitagliptin.

Acute Renal Failure
Assessment of renal function is recommended prior to initiating Sitagliptin and periodically thereafter. A dosage adjustment is recommended in patients with moderate or severe renal impairment and in patients with ESRD requiring haemodialysis or peritoneal dialysis. Caution should be used to ensure that the correct dose of Sitagliptin is prescribed for patients with moderate (creatinine clearance ≥30 to <50 mL/min) or severe (creatinine clearance <30 mL/min) renal impairment.

There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. A subset of these reports involved patients with renal impairment, some of whom were prescribed inappropriate doses of Sitagliptin. A return to baseline levels of renal impairment has been observed with supportive treatment and discontinuation of potentially causative agents. Consideration can be given to cautiously reinitiating Sitagliptin if another etiology is deemed likely to have precipitated the acute worsening of renal function.

Sitagliptin has not been found to be nephrotoxic in preclinical studies at clinically relevant doses, or in clinical trials.

Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues
When Sitagliptin was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia.

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.
Angioedema has also been reported with other DPP-4 inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with Sitagliptin.

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.

Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Sitagliptin or any other anti-diabetic drug.

4.5 Drugs interactions
Digoxin
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 100 mg Sitagliptin for 10 days. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or Sitagliptin is recommended.

Insulin Secretagogues or Insulin
Coadministration of Sitagliptin with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)
Pregnancy
Pregnancy Category B:
Reproduction studies have been performed in rats and rabbits. Doses of Sitagliptin up to 125 mg/kg (approximately 12 times the human exposure at the maximum recommended human dose) did not impair fertility or harm the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Sitagliptin administered to pregnant female rats and rabbits from gestation day 6 to 20 (organogenesis) was not teratogenic at oral doses up to 250 mg/kg (rats) and 125 mg/kg (rabbits), or approximately 30- and 20-times human exposure at the maximum recommended human dose (MRHD) of 100 mg/day based on AUC comparisons. Higher doses increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100 times human exposure at the MRHD.

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 decreased body weight in male and female offspring at 1000 mg/kg. No functional or behavioral toxicity was observed in offspring of rats.

Placental transfer of Sitagliptin administered to pregnant rats was approximately 45% at 2 hours and 80% at 24 hours post dose. Placental transfer of Sitagliptin administered to pregnant rabbits was approximately 66% at 2 hours and 30% at 24 hours.

Nursing Mothers
Sitagliptin is secreted in the milk of lactating rats at a milk to plasma ratio of 4:1. It is not known whether Sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Sitagliptin is administered to a nursing woman.

Lactation
There is no information regarding the presence of Sitagliptin in human milk, the effects on the breastfed infant, or the effects on milk production. Sitagliptin is present in rat milk and therefore possibly present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Sitagliptin and any potential adverse effects on the breastfed infant from Sitagliptin or from the underlying maternal condition.

Pediatric Use
Safety and effectiveness of Sitagliptin in pediatric patients under 18 years of age have not been established.

Geriatric Use
Of the total number of subjects (N=3884) in pre-approval clinical safety and efficacy studies of Sitagliptin, 725 patients were 65 years and over, while 61 patients were 75 years and over. No overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. While this and other reported clinical experience have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly, and it may be useful to assess renal function in these patients prior to initiating dosing and periodically thereafter.

Renal Impairment
Sitagliptin is excreted by the kidney, and sitagliptin exposure is increased in patients with renal impairment. Lower dosages are recommended in patients with eGFR less than 45 mL/min/1.73 m2 (Moderate and severe renal impairment, as well as in ESRD patients requiring dialysis).

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
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In controlled clinical studies as both monotherapy and combination therapy with Metformin, Pioglitazone, or Rosiglitazone and Metformin, the overall incidence of adverse reactions, hypoglycemia, and discontinuation of therapy due to clinical adverse reactions with Sitagliptin were similar to placebo. In combination with Glimepiride, with or without Metformin, the overall incidence of clinical adverse reactions with Sitagliptin was higher than with placebo, in part related to a higher incidence of hypoglycemia (see Table 3); the incidence of discontinuation due to clinical adverse reactions was similar to placebo.

Two placebo-controlled monotherapy studies, one of 18- and one of 24-week duration, included patients treated with Sitagliptin 100 mg daily, Sitagliptin 200 mg daily, and placebo. Five placebo-controlled add-on combination therapy studies were also conducted: one with Metformin; one with Pioglitazone; one with Metformin and Rosiglitazone; one with Glimepiride (with or without Metformin); and one with insulin (with or without Metformin). In these trials, patients with inadequate glycemic control on a stable dose of the background therapy were randomized to add-on therapy with Sitagliptin 100 mg daily or placebo. The adverse reactions, excluding hypoglycemia, reported regardless of investigator assessment of causality in ≥5% of patients treated with Sitagliptin 100 mg daily and more commonly than in patients treated with placebo, are shown in Table 1 for the clinical trials of at least 18 weeks duration. Incidences of hypoglycemia are shown in Table 3.

Table 1. Placebo-Controlled Clinical Studies of Sitagliptin Monotherapy or Add-on Combination Therapy with Pioglitazone, Metformin + Rosiglitazone, or Glimepiride +/- Metformin: Adverse Reactions (Excluding Hypoglycemia) Reported in ≥ 5% of Patients and More Commonly than in Patients Given Placebo, Regardless of Investigator Assessment of Causality†

	Number of Patients (%)	
Monotherapy (18 or 24 weeks)	**Sitagliptin 100 mg**	**Placebo**
	N = 443	N = 363
Nasopharyngitis	23 (5.2)	12 (3.3)
Combination with Pioglitazone (24weeks)	**Sitagliptin 100 mg + Pioglitazone**	**Placebo + Pioglitazone**
	N = 175	N = 178
Upper Respiratory Tract Infection	11 (6.3)	6 (3.4)
Headache	9 (5.1)	7 (3.9)
Combination with Metformin +Rosiglitazone (18 weeks)	**Sitagliptin 100 mg + Metformin + Rosiglitazone**	**Placebo + Metformin + Rosiglitazone**
	N = 181	N = 97
Upper Respiratory Tract Infection	10 (5.5)	5 (5.2)
Nasopharyngitis	11 (6.1)	4 (4.1)
Combination with Glimepiride(+/- Metformin) (24 weeks)	**Sitagliptin 100 mg + Glimepiride (+/- Metformin)**	**Placebo + Glimepiride (+/- Metformin)**
	N = 222	N = 219
Nasopharyngitis	14 (6.3)	10 (4.6)
Headache	13 (5.9)	5 (2.3)

† Intent-to-treat population

In the 24-week study of patients receiving Sitagliptin as add-on combination therapy with Metformin, there were no adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo.

In the 24-week study of patients receiving Sitagliptin as add-on therapy to insulin (with or without Metformin), there were no adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo, except for hypoglycemia (see Table 3).

In the study of Sitagliptin as add-on combination therapy with Metformin and Rosiglitazone (Table 1), through Week 54 the adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients treated with Sitagliptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (Sitagliptin, 15.5%; placebo, 6.2%), nasopharyngitis (11.0%, 9.3%), peripheral edema (8.3%, 5.2%), and headache (5.5%, 4.1%). In a pooled analysis of the two monotherapy studies, the add-on to Metformin study, and the add-on to Pioglitazone study, the incidence of selected gastrointestinal adverse reactions in patients treated with Sitagliptin was as follows: abdominal pain (Sitagliptin 100 mg, 2.3%; placebo, 2.1%), nausea (1.4%, 0.6%), and diarrhea (3.0%, 2.3%).

In an additional, 24-week, placebo-controlled factorial study of initial therapy with Sitagliptin in combination with Metformin, the adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients are shown in Table 2.

Table 2. Initial Therapy with Combination of Sitagliptin and Metformin: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥ 5% of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Metformin alone, Sitagliptin alone, and Placebo)†

	Number of Patients (%)			
	Placebo	Sitagliptin 100 mg QD	Metformin 500 or 1000 mg bid ††	Sitagliptin 50 mg bid + Metformin 500 or 1000 mg bid ††
	N = 176	N = 179	N = 364††	N = 372††
Upper Respiratory Infection	9 (5.1)	8 (4.5)	19 (5.2)	23 (6.2)
Headache	5 (2.8)	2 (1.1)	14 (3.8)	22 (5.9)

† Intent-to-treat population.
†† Data pooled for the patients given the lower and higher doses of Metformin.

In a 24-week study of initial therapy with Sitagliptin in combination with Pioglitazone, there were no adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients and more commonly than in patients given Pioglitazone alone.

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

In a pooled analysis of 19 double-blind clinical trials that included data from 10,246 patients randomized to receive Sitagliptin 100 mg/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).

Hypoglycemia
In all (N=9) studies, adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia. A concurrent blood glucose measurement was not required although most (74%) reports of hypoglycemia were accompanied by a blood glucose measurement ≤70 mg/dL. When Sitagliptin was co-administered with a sulfonylurea or with insulin, the percentage of patients with at least one adverse reaction of hypoglycemia was higher than in the corresponding placebo group (Table 3).

Table 3 Incidence and Rate of Hypoglycemia† in Placebo-Controlled Clinical Studies when Sitagliptin was used as Add-On Therapy to Glimepiride (with or without Metformin) or Insulin (with or without Metformin), Regardless of Investigator Assessment of Causality

Add-On to Glimepiride (+/- Metformin) (24 weeks)	**Sitagliptin 100 mg + Glimepiride (+/- Metformin)**	**Placebo + Glimepiride (+/- Metformin)**
	N = 222	N = 219
Overall (%)	27 (12.2)	4 (1.8)
Rate (episodes/patient-year)‡	0.59	0.24
Severe (%)§	0 (0.0)	0 (0.0)
Add-On to Insulin (+/- Metformin) (24 weeks)	**Sitagliptin 100 mg + Insulin (+/- Metformin)**	**Placebo + Insulin (+/- Metformin)**
	N = 322	N = 319
Overall (%)	50 (15.5)	25 (7.8)
Rate (episodes/patient-year) ‡	1.06	0.51
Severe (%)§	2 (0.6)	1 (0.3)

† Adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required; intent-to-treat population.
‡ Based on total number of events (i.e., a single patient may have had multiple events).
§ Severe events of hypoglycemia were defined as those events requiring medical assistance or exhibiting depressed level/loss of consciousness or seizure.

In a pooled analysis of the two monotherapy studies, the add-on to Metformin study, and the add-on to Pioglitazone study, the overall incidence of adverse reactions of hypoglycemia was 1.2% in patients treated with Sitagliptin 100 mg and 0.9% in patients treated with placebo.

In the study of Sitagliptin as add-on combination therapy with Metformin and Rosiglitazone, the overall incidence of hypoglycemia was 2.2% in patients given add-on Sitagliptin and 0.0% in patients given add-on placebo through Week 18. Through Week 54, the overall incidence of hypoglycemia was 3.9% in patients given add-on Sitagliptin and 1.0% in patients given add-on placebo.

In the 24-week, placebo-controlled factorial study of initial therapy with Sitagliptin in combination with Metformin, the incidence of hypoglycemia was 0.6% in patients given placebo, 0.6% in patients given Sitagliptin alone, 0.8% in patients given Metformin alone, and 1.6% in patients given Sitagliptin in combination with Metformin.

In the study of Sitagliptin as initial therapy with Pioglitazone, one patient taking Sitagliptin experienced a severe episode of hypoglycemia. There were no severe hypoglycemia episodes reported in other studies except in the study involving co-administration with insulin.

Laboratory Tests
Across clinical studies, the incidence of laboratory adverse reactions was similar in patients treated with Sitagliptin 100 mg compared to patients treated with placebo. A small increase in white blood cell count (WBC) was observed due to an increase in neutrophils. This increase in WBC (of approximately 200 cells/microL vs placebo, in four pooled placebo-controlled clinical studies, with a mean baseline WBC count of approximately 6600 cells/microL) is not considered to be clinically relevant. In a 12-week study of 91 patients with chronic renal insufficiency, 37 patients with moderate renal insufficiency were randomized to Sitagliptin 50 mg daily, while 14 patients with the same magnitude of renal impairment were randomized to placebo. Mean (SE) increases in serum creatinine were observed in patients treated with Sitagliptin [0.12 mg/dL (0.04)] and in patients treated with placebo [0.07 mg/dL (0.07)]. The clinical significance of this added increase in serum creatinine relative to placebo is not known.

Postmarketing Experience
Additional adverse reactions have been identified during postapproval use of Sitagliptin 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 a causal relationship to drug exposure.

Hypersensitivity reactions including Arthralgia, anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis; worsening renal function, including acute renal failure (sometimes requiring dialysis); constipation; vomiting; headache, bullous pemphigoid, myalgia; pain in extremity; back pain; mouth ulceration; stomatitis; rabdomyolysis.

4.9 Overdose
During controlled clinical trials in healthy subjects, single doses of up to 800 mg Sitagliptin were administered. Maximal mean increases in QTc of 8.0 msec were observed in one study at a dose of 800 mg Sitagliptin, a mean effect that is not considered clinically important. 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 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 as indicated by the patient's clinical status. 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.

5 Pharmacological properties
5.1 Mechanism of Action
Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by Sitagliptin, thereby increasing and prolonging the action of these 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. These hormones are rapidly inactivated by the enzyme, DPP-4. 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. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, Sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity in vitro at concentrations approximating those from therapeutic doses.

5.2 Pharmacodynamic properties
General
In patients with type 2 diabetes, administration of Sitagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased responsiveness of insulin release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin with the decrease in glucagon was associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

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. Coadministration of Sitagliptin and Metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not Metformin, increased active GIP concentrations. It is unclear how these findings relate to changes in glycemic control in patients with type 2 diabetes. In studies with healthy subjects, Sitagliptin did not lower blood glucose or cause hypoglycemia.

Cardiac Electrophysiology
In a randomized, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of Sitagliptin 100 mg, Sitagliptin 800 mg (8 times the recommended dose), and placebo. At the recommended dose of 100 mg, there was no effect on the QTc interval obtained at the peak plasma concentration, or at any other time during the study. Following the 800 mg dose, the maximum increase in the placebo-corrected mean change in QTc from baseline was observed at 3 hours postdose and was 8.0 msec. This increase is not considered to be clinically significant. At the 800 mg dose, peak Sitagliptin. plasma concentrations were approximately 11 times higher than the peak concentrations following a 100 mg dose.

In patients with type 2 diabetes administered Sitagliptin 100 mg (N=81) or Sitagliptin 200 mg (N=63) daily, there were no meaningful changes in QTc interval based on ECG data obtained at the time of expected peak plasma concentration.

5.3 Pharmacokinetic properties
The pharmacokinetics of Sitagliptin has 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 postdose. 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 was generally similar in healthy subjects and in patients with type 2 diabetes.

Absorption
The absolute bioavailability of Sitagliptin is approximately 87%. Because coadministration 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
Approximately 79% of Sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination.

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.

Excretion
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.

Special Populations
Renal Insufficiency

An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal impairment with eGFR of 30 to less than 45 mL/min/1.73 m2, and an approximately 4-fold increase was observed in patients with severe renal impairment, including patients with ESRD on hemodialysis, as compared to normal healthy control subjects.

Hepatic Insufficiency
In patients with moderate hepatic insufficiency (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 insufficiency.
There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score >9).

Effects of Age, Body Mass Index (BMI), Gender, and Race

Based on a population pharmacokinetic analysis or a composite analysis of available pharmacokinetic data, BMI, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of sitagliptin. When the effects of age on renal function are taken into account, age alone 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.

Drug Interactions
In Vitro Assessment of Drug Interactions
Sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4. Sitagliptin is a p-glycoprotein substrate but does not inhibit p-glycoprotein mediated transport of digoxin. Based on these results, Sitagliptin is considered unlikely to cause interactions with other drugs that utilize these pathways.

Sitagliptin is not extensively bound to plasma proteins. Therefore, the propensity of Sitagliptin to be involved in clinically meaningful drug-drug interactions mediated by plasma protein binding displacement is very low.

In Vivo Assessment of Drug Interactions
Effects of Sitagliptin on Other Drugs
In clinical studies, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, digoxin, warfarin, or an oral contraceptive (ethinyl estradiol and norethindrone) (Table 4), providing in vivo evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, P-gp, and organic cationic transporter (OCT).

Table 4: Effect of Sitagliptin on Systemic Exposure of Coadministered Drugs

Coadministered Drug	Dose of Coadministered Drug*	Dose of Sitagliptin*	Geometric Mean Ratio (ratio with/without sitagliptin) No Effect = 1.00		
				AUC†	C_{max}
Digoxin	0.25 mg‡ once daily for 10 days	100 mg‡ once daily for 10 days	Digoxin	1.11§	1.18
Glyburide	1.25 mg	200 mg‡ once daily for 6 days	Glyburide	1.09	1.01
Simvastatin	20 mg	200 mg‡ once daily for 5 days	Simvastatin	0.85¶	0.80
			Simvastatin Acid	1.12¶	1.06
Rosiglitazone	4 mg	200 mg‡ once daily for 5 days	Rosiglitazone	0.98	0.99
Warfarin	30 mg single dose on day 5	200 mg‡ once daily for 11 days	S(-) Warfarin	0.95	0.89
			R(+) Warfarin	0.99	0.89
Ethinyl estradiol and norethindrone	21 days once daily of 35 µg ethinyl estradiol with norethindrone 0.5 mg x 7 days, 0.75 mg x 7 days, 1.0 mg x 7 days	200 mg‡ once daily for 21 days	Ethinyl estradiol	0.99	0.97
			Norethindrone	1.03	0.98
Metformin HCl	1000 mg‡ twice daily for 14 days	50 mg‡ twice daily for 7 days	Metformin	1.02#	0.97

* All doses administered as single dose unless otherwise specified.
† AUC is reported as AUC0-∞ unless otherwise specified.
‡ Multiple doses.
§AUC0-24hr.
¶ AUC0-last.
# AUC0-12hr.

Effects of Other Drugs on Sitagliptin
Clinical data described below suggest that sitagliptin is not susceptible to clinically meaningful interactions by coadministered medications (Table 5).

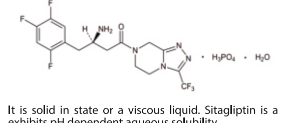
Table 5: Effect of Coadministered Drugs on Systemic Exposure of Sitagliptin

Coadministered Drug	Dose of Coadministered Drug*	Dose of Sitagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
				AUC†	C_{max}
Cyclosporine	600 mg once daily	100 mg once daily	Sitagliptin	1.29	1.68
Metformin HCl	1000 mg‡ twice daily for 14 days	50 mg‡ twice daily for 7 days	Sitagliptin	1.02§	1.05

* All doses administered as single dose unless otherwise specified.
† AUC is reported as AUC0-∞ unless otherwise specified.
‡ Multiple dose.
§ AUC0-12hr.

6. Nonclinical properties
6.1 Animal toxicology or Pharmacology
Carcinogenesis, Mutagenesis, Impairment of Fertility
A two-year carcinogenicity study was conducted in male and female rats given oral doses of Sitagliptin of 50, 150, and 500 mg/kg/day. There was an increased incidence of combined liver adenoma/carcinoma in males and females and of liver carcinoma in females at 500 mg/kg. This dose results in exposures approximately 60 times the human exposure at the maximum recommended daily adult human dose (MRHD) of 100 mg/day based on AUC comparisons. Liver tumors were not observed at 150 mg/kg, approximately 20 times the human exposure at the MRHD. A two-year carcinogenicity study was conducted in male and female mice given oral doses of Sitagliptin of 50, 125, 250, and 500 mg/kg/day. There was no increase in the incidence of tumors in any organ up to 500 mg/kg, approximately 70 times human exposure at the MRHD. Sitagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a Chinese hamster ovary (CHO) chromosome aberration assay, an in vitro cytogenetics assay in CHO, an in vitro rat hepatocyte DNA alkaline elution assay, and an in vivo micronucleus assay. In rat fertility studies with oral gavage doses of 125, 250, and 1000 mg/kg, males were treated for 4 weeks prior to mating, during mating, up to scheduled termination (approximately 8 weeks total) and females were treated 2 weeks prior to mating through gestation day 7. No adverse effect on fertility was observed at 125 mg/kg (approximately 12 times human exposure at the MRHD of 100 mg/day based on AUC comparisons). At higher doses, nondose-related increased resorptions in females were observed (approximately 25- and 100-times human exposure at the MRHD based on AUC comparison).

7. Description
Sitagliptin phosphate monohydrate is described chemically as
7-[(3R)-3-amino-1-oxo-4-(2,4,5trifluorophenyl)btyl]
-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate.
The empirical formula is $C_{16}H_{15}F_6N_5O•H_3PO_4•H_2O$ and the molecular weight is 523.32. The structural formula is: :



It is solid in state or a viscous liquid. Sitagliptin is a white to off-powder and exhibits pH dependent aqueous solubility.
It is soluble in water and N,N-dimethyl formamide, slightly soluble in methanol, soluble in ethanol, acetone and acetonitrile and insoluble in isopropanol and isopropyl acetate.

8. Pharmaceutical particulars

8.1 Incompatibilities
Not Applicable

8.2 Shelf Life:
24 Months

8.3 Packaging Information
Blister pack of 10 Tablets

8.4 Storage and handling instructions:
Store below 30°C. Protected from moisture.

9. Patient counselling information
Advise the patient to read the prescribing information (Medication Guide).

Pancreatitis
Inform patients that acute pancreatitis has been reported during postmarketing use of Sitagliptin. Inform patients that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to promptly discontinue Sitagliptin and contact their physician if persistent severe abdominal pain occurs.

Heart Failure
Inform patients of the signs and symptoms of heart failure. Before initiating Sitagliptin, ask patients about a history of heart failure or other risk factors for heart failure including moderate to severe renal impairment. Instruct patients to contact their health care provider as soon as possible if they experience symptoms of heart failure, including increasing shortness of breath, rapid increase in weight or swelling of the feet.

Hypoglycemia
Inform patients that the incidence of hypoglycemia is increased when Sitagliptin is added to a sulfonylurea or insulin. Explain to patients receiving Sitagliptin in combination with these medications the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development.

Hypersensitivity Reactions
Inform patients that allergic reactions have been reported during postmarketing use of Sitagliptin. If symptoms of allergic reactions (including rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking Sitagliptin and seek medical advice promptly

Severe and Disabling Arthralgia
Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs.

Bullous Pemphigoid
Inform patients that bullous pemphigoid may occur with this class of drugs. Instruct patients to seek medical advice if blisters or erosions occur.

10. Details of Manufacturer
Manufactured in India by
Windlas Biotech Limited
(Plant-2), Khasra No. 141 to 143
& 145, Mohabewala Industrial Area,
Dehradun-248110, Uttarakhand.

11. Details of Permission or Licence Number With Date
Licence No.: 34/UA/2013; Dated: 03-02-2022

12. Date of Revision
April 2022

Marketed By:
Bioessentia LifeSciences
108, Sai Priya Grandeur Appt,
Doddathogur, ECity, Bengaluru,
Bangalore-Karnataka-560100
TM- Trademark applied for

Front

Back

Leaflet
Unfolded Size: 120 x 350 mm
Black 100