Sitagliptin

Siptin 25®

25 mg Film coated tablet
Antihyperglycemic Agent

PRODUCT DESCRIPTION:
Orange, round, biconvex film-coated tablet.

FORMULATION/COMPOSITION:
Each film-coated tablet contains:
Sitagliptin Phosphate Monohydrate equivalent to Sitagliptin.....25 mg

INDICATIONS:
For adult patients with type 2 diabetes mellitus, Siptin (Sitagliptin) tablets are indicated to improve glycaemic 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 glycaemic control.
- A sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic 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 glycaemic control.

As triple oral therapy in combination with:
- A sulphonylurea and Metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic 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 glycaemic control.

Siptin is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control.

DOSAGE AND ADMINSTRATION:
The dose is 100 mg sitagliptin once daily. When used in combination with metformin and/or a PPAR-γ agonist, the dose of metformin and/or PPAR-γ agonist should be maintained, and Siptin administered concomitantly.
When Siptin is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia. If a dose of Siptin 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
Sitagliptin dosing is based on renal function. No dose adjustment is required for GFR ≥45 mL/min. For moderate renal impairment (GFR ≥30 to <45 mL/min), the dose is 50 mg once daily. For severe renal impairment or ESRD (GFR <30 mL/min), the dose is 25 mg once daily, irrespective of dialysis timing. Renal function should be assessed before initiation and periodically thereafter.

Hepatic Impairment
No dose adjustment is necessary for patients with mild to moderate hepatic impairment. Siptin 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.

Children and adolescents
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 tablet can be taken with or without food.

CONTRAINDICATIONS:
Hypersensitivity to the active ingredient or any excipients (See sections Special warnings and precautions for use/ Interaction with other medicinal products and other forms of interaction)

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

General
Siptin (Sitagliptin) should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Acute Pancreatitis
DPP-4 inhibitors like Sitagliptin (e.g., Siptin) may rarely cause acute pancreatitis. Patients should report severe, persistent abdominal pain. Discontinue if suspected; do not restart if confirmed. Caution should be exercised in patients with a history of pancreatitis.

Hypoglycaemia when used in combination with other anti-hyperglycaemic medicinal products
With Siptin (Sitagliptin), hypoglycaemia risk is minimal when used alone or with Metformin or PPARγ agonists, similar to placebo. However, the risk increases when combined with insulin or Sulphonylureas; therefore, dose reduction of these agents should be considered to minimize hypoglycaemia.

Renal impairment
Siptin is mainly eliminated via the kidneys; therefore, dose adjustment is required in patients with GFR <45 mL/min, including those with ESRD (End-Stage Renal Disease) on haemodialysis or peritoneal dialysis, to maintain appropriate plasma levels. When used in combination therapy, the prescribing guidance and renal precautions for the co-administered antidiabetic medicines should also be carefully considered.

Hypersensitivity reactions
Post-marketing reports with Sitagliptin (e.g., Siptin) include rare but serious hypersensitivity reactions such as anaphylaxis, angioedema, and severe skin reactions (e.g., Stevens-Johnson syndrome), often occurring within the first 3 months or even after the first dose. If suspected, discontinue treatment, evaluate other causes, and initiate alternative antidiabetic therapy.

Bullous pemphigoid
Post-marketing cases of Bullous pemphigoid have been reported with DPP-4 inhibitors including Sitagliptin (e.g., Siptin); discontinue if suspected.

Sodium
This medicinal product is essentially sodium-free, containing less than 1 mmol sodium (23 mg) per tablet.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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, Sitagliptin is minimally metabolised mainly by CYP3A4 (with some contribution from CYP2C8), and in normal renal function this pathway has a minor role in clearance. However, in severe renal impairment or End-Stage Renal Disease, metabolism may become more relevant, and potent CYP3A4 inhibitors (e.g., Ketoconazole, Itraconazole, Ritonavir, Clarithromycin) could potentially affect its pharmacokinetics, although this has not been clinically studied.
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 twice-daily doses 1,000 mg Metformin with Sitagliptin does not meaningfully alter sitagliptin pharmacokinetics in patients with type 2 diabetes.
Ciclosporin: In a study, co-administration of Ciclosporin (600 mg single dose) with Sitagliptin (100 mg single dose) increased sitagliptin AUC by ~29% and Cmax by ~68%. These changes were not clinically meaningful, and renal clearance was unchanged; therefore, significant interactions with other P-glycoprotein inhibitors are not expected.

Effects of sitagliptin on other medicinal products
Digoxin: Co-administration of Sitagliptin with Digoxin results in a slight increase in digoxin exposure (AUC ~11% and Cmax ~18%). No dose adjustment is required, but patients at risk of digoxin toxicity should be monitored during concomitant use.
In vitro data show Sitagliptin does not inhibit or induce Cytochrome P450 enzymes. Clinically, it does not meaningfully affect drugs such as Metformin, Glyburide, Simvastatin, Rosiglitazone, Warfarin, or oral contraceptives, indicating low interaction potential via CYP3A4, CYP2C8, CYP2C9, or OCT pathways. It may act as a mild P-glycoprotein inhibitor in vivo.

USE IN SPECIFIC POPULATIONS:

Pregnancy, Lactation and Fertility

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, Siptin should not be used during pregnancy.

Lactation
It is unknown whether sitagliptin is excreted in human breast milk. Animal studies have shown excretion of sitagliptin in breast milk. Siptin 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Siptin 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.

UNDESIRABLE EFFECTS

Summary of the safety profile
Serious adverse reactions including pancreatitis and hypersensitivity reactions have been reported. Hypoglycaemia has been reported in combination with sulphonylurea (4.7 %-13.8 %) and insulin (9.6 %) **(see section: Special warnings and precautions for use).**

Tabulated list of adverse reactions
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).

System organ class	Adverse reaction	Frequency
Blood and lymphatic system disorders	thrombocytopenia	Rare
Immune system disorders	hypersensitivity reactions including anaphylactic responses*,†	Frequency not known
Metabolism and nutrition disorders	hypoglycaemia†	Common
Nervous system disorders	headache	Common
	dizziness	Uncommon
Respiratory, thoracic and mediastinal disorders	interstitial lung disease*	Frequency not known
Gastrointestinal disorders	constipation	Uncommon
	vomiting*	Frequency not known
	acute pancreatitis*,†,‡	Frequency not known
	fatal and non-fatal haemorrhagic and necrotizing pancreatitis*,†	Frequency not known
Skin and subcutaneous tissue disorders	pruritus*	Uncommon
	angioedema*,†	Frequency not known
	rash*,†	Frequency not known
	urticaria*,†	Frequency not known
	cutaneous vasculitis*,†	Frequency not known
	exfoliative skin conditions including Stevens-Johnson syndrome*,†	Frequency not known
	bullous pemphigoid*	Frequency not known
Musculoskeletal and connective tissue disorders	arthralgia*	Frequency not known
	myalgia*	Frequency not known
	back pain*	Frequency not known
	arthropathy*	Frequency not known
Renal and urinary disorders	impaired renal function*	Frequency not known
	acute renal failure*	Frequency not known

*Adverse reactions were identified through post-marketing surveillance.
† See section: Special warnings and precautions for use.
‡ See TECOS Cardiovascular Safety Study below.

Description of selected adverse reactions

With Sitagliptin, common adverse events include upper respiratory tract infection and nasopharyngitis (≥5%). Less frequent effects include osteoarthritis and pain in extremities.

In combination therapy, additional effects may occur: hypoglycaemia (especially with sulphonylurea + metformin), influenza (with insulin ± metformin), gastrointestinal effects such as nausea, vomiting, diarrhoea, constipation, and flatulence (with metformin/pioglitazone combinations), peripheral oedema (with pioglitazone), somnolence, and dry mouth (with insulin combinations).

Paediatric population

In clinical trials with sitagliptin in paediatric patients with type 2 diabetes mellitus aged 10 to17 years, the profile of adverse reactions was comparable to that observed in adults.

TECOS Cardiovascular Safety Study

Sitagliptin (with background therapy) showed a similar overall rate of serious adverse events compared with placebo. Severe hypoglycaemia rates were comparable between groups, slightly higher mainly in patients using insulin and/or Sulphonylureas. Confirmed pancreatitis was rare and occurred at a similar low rate in both sitagliptin and placebo groups.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions

OVERDOSE

In healthy subjects, single doses of Sitagliptin up to 800 mg showed only minimal, non–clinically relevant QTc changes, with no dose-related toxicity in multiple-dose studies up to 600 mg/day (10 days) and 400 mg/day (28 days).

In overdose cases, supportive management is recommended, including gastrointestinal decontamination, clinical monitoring (including ECG), and symptomatic treatment. Sitagliptin is only modestly removed by haemodialysis (~13.5% over 344 hours); prolonged dialysis may be considered if needed, while the effect of peritoneal dialysis is unknown.

PHARMACOLOGICAL PROPERTIES:

Pharmacodynamic properties:

Pharmacotherapeutic group: Drugs used in diabetes, DPP-4 inhibitors, ATC code: A10BH01.

Mechanism of action

Sitagliptin is an oral anti-hyperglycaemic agent that inhibits DPP-4, increasing active incretin hormones (GLP-1 and GIP). This enhances glucose-dependent insulin secretion from pancreatic beta cells and suppresses glucagon release from alpha cells, thereby reducing hepatic glucose production and lowering fasting and postprandial glucose levels. The improvement in glycaemic control leads to reduced HbA1c without causing hypoglycaemia under normal glucose conditions. It works only when glucose levels are elevated, making its action physiologically regulated. It is a highly selective DPP-4 inhibitor with no clinically relevant inhibition of DPP-8 or DPP-9 at therapeutic doses, supporting a favorable safety profile.

In healthy subjects, Sitagliptin alone increases active GLP-1 levels, while Metformin increases both active and total GLP-1 (Glucagon-like Peptide-1) to a similar extent. When used together, they produce an additive increase in active GLP-1 concentrations. Sitagliptin also increases active GIP levels, whereas metformin does not affect GIP (Glucose-dependent Insulinotropic Polypeptide).

Clinical efficacy and safety

Overall, sitagliptin improved glycaemic control when used as monotherapy or in combination treatment in adult patients with type 2 diabetes

In clinical trials, sitagliptin as monotherapy improved glycaemic control with significant reductions in haemoglobin A1c (HbA1c) and fasting and postprandial glucose. Reduction in fasting plasma glucose (FPG) was observed at three weeks, the first time point at which FPG was measured. The observed incidence of hypoglycaemia in patients treated with sitagliptin was similar to placebo. Body weight did not increase from baseline with sitagliptin therapy.

Improvements in surrogate markers of beta-cell function, including HOMA-β (Homeostasis Model Assessment of β-cell function), proinsulin-to-insulin ratio, and measures of beta-cell responsiveness from the frequently sampled meal tolerance test were observed.

Paediatric population

The European Medicines Agency has waived the obligation to submit study results with Sitagliptin in all subsets of the paediatric population for type 2 diabetes mellitus.

Pharmacokinetic properties:

Absorption

Following oral administration of a 100 mg dose of Sitagliptin in healthy subjects, it is rapidly absorbed with peak plasma levels (Tmax) occurring within 1–4 hours. The mean plasma AUC is 8.52 μM·hr and Cmax is 950 nM, with an absolute bioavailability of approximately 87%.

Food has no clinically relevant effect on pharmacokinetics, so it can be taken with or without meals. Exposure (AUC) increases in a dose-proportional manner, while Cmax increases more than proportionally and C24hr less than proportionally with dose.

Distribution

The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 litres. 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 oral administration of a radiolabeled dose of Sitagliptin, about 87% of radioactivity is recovered in urine and 13% in faeces within one week, indicating predominant renal elimination. The terminal half-life is approximately 12.4 hours, with minimal accumulation on repeated dosing. Renal clearance is ~350 mL/min, involving active tubular secretion.

Sitagliptin is a substrate of human organic anion transporter-3 (hOAT3) and P-glycoprotein, but not of OCT2, OAT1, or PEPT transporters. Although P-gp inhibition by Ciclosporin does not reduce renal clearance, sitagliptin shows no clinically relevant inhibition of OAT3 or P-gp at therapeutic levels and may only act as a mild P-gp inhibitor (e.g., slight increase in digoxin exposure).

STORAGE CONDITION:

Store at or below 30°C

AVAILABILITY:

Strip pack x 10's (Box of 150's)

MANUFACTURED BY:

Quest Pharmaceuticals Pvt. Ltd.
Chhatapipara, Bara, Nepal

MARKETING AUTHORIZATION HOLDER:

Quest Pharmaceuticals Pvt. Ltd.
Daan Sadan, Teku, Kathmandu, Nepal