1.4 Product Information

1.4.1 Prescribing Information

(SUMMARY OF PRODUCT CHARACTERISTICS)

1. Name of the Finished Pharmaceutical Product

1.1 Product name

Sita Tablet 100mg

1.2 Strength

100mg

1.3 Pharmaceutical form

Film coated tablet

2. Qualitative and Quantitative Composition

2.1 Qualitative Declaration

Sitagliptin Phosphate monohydrate

2.2 Quantitative Declaration

Each film coated tablet contains:
Sitagliptin Phosphate monohydrate equivalent to
Sitagliptin 100mg

3. Pharmaceutical Form

Light pearl orange oval biconvex with cut film coated tablet.

4. Clinical Particulars:

4.1 Therapeutic Indications

For adult patients with type 2 diabetes mellitus, Sitagliptin is indicated to improve glycaemic control:

As monotherapy

iii) 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

v) Metformin when diet and exercise plus Metformin alone do not provide adequate glycaemic control.

vi) 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

i) A sulphonylurea and Metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

ii) 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.

Sita 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 glycaemic control.

4.2 Posology and Method of Administration

The dose of Sitagliptin is 100 mg once daily. When Sita is used in combination with Metformin and/or a PPARγ agonist, the dose of Metformin and/or PPARγ agonist should be maintained, and Sitagliptin administered concomitantly.

When Sitagliptin 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 Sitagliptin 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 product, its conditions for use in patients with renal impairment should be checked.

For patients with mild renal impairment (creatinine clearance [CrCl] ≥50 ml/min), no dose adjustment for Sita is required.

For patients with moderate renal impairment (CrCl ≥30 to <50 mL/min), the dose of Sita is 50 mg once daily.

For patients with severe renal impairment (CrCl <30 mL/min) or with end-stage renal disease (ESRD) requiring haemodialysis or peritoneal dialysis, the dose of Sita is 25 mg once daily. Sita 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 Sita and periodically thereafter.

Hepatic impairment

No dose adjustment is necessary for patients with mild to moderate hepatic impairment. Sita has not been studied in patients with severe hepatic impairment.

Elderly

No dose adjustment is necessary based on age. Limited safety data is available in patients ≥75 years of age and care should be exercised.

Paediatric population

Sita is not recommended for use in children below 18 years of age due to a lack of data on its safety and efficacy.

4.3 Method of Administration

Oral .

4.4 Contra Indications

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

4.5 Special Warning and Precautions for Use

General

Sita should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Pancreatitis

In post-marketing experience there have been spontaneously reported adverse reactions of acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of Sitagliptin (with or without

supportive treatment), but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, Sita and other potentially suspect medicinal products should be discontinued.

Hypoglycaemia when used in combination with other anti-hyperglycaemic agents

In clinical trials of Sita as monotherapy and as part of combination therapy with medicinal products not known to cause hypoglycaemia (i.e. Metformin and/or a PPARγ agonist), rates of hypoglycaemia reported with Sitagliptin were similar to rates in patients taking placebo.When Sitagliptin was added to a sulphonylurea or to insulin, the incidence of hypoglycaemia was increased over that of placebo. Therefore, to reduce the risk of hypoglycaemia, a lower dose of sulphonylurea or insulin may be considered.

Renal impairment

Sita is renally excreted. To achieve plasma concentrations of Sita 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 haemodialysis or peritoneal dialysis. When considering the use of Sitagliptin in combination with another anti-diabetic product, its conditions for use in patients with renal impairment should be checked.

Hypersensitivity reactions

Postmarketing reports of serious hypersensitivity reactions in patients treated with Sita 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 Sita, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue Sita, assess for other potential causes for the event, and institute alternative treatment for diabetes

4.6 Additional Information on Special Populations

Not Applicable

4.7 Paediatric Population

Not Applicable

4.8 Fertility, Pregnancy and Lactation

Use during pregnancy

There are no adequate data from the use of Sita 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, Sita should not be used during pregnancy.

Use during lactation

It is unknown whether Sitagliptin is excreted in human breast milk. Animal studies have shown excretion of Sitagliptin in breast milk. Sita should not be used during breast-feeding.

4.9 Effects on ability to drive and use machines

None .

4.10Undesirable Effects

The incidence of selected gastrointestinal adverse experiences in patients treated with Sitagliptin were: abdominal pain, nausea, vomiting and diarrhea.

Add-on Combination with Sulfonylureas:

More common side effect is hypoglycemia

Add-on Combination with a Metformin and PPARγ agonist:

Common side effects are headache, diarrhea, nausea, hypoglycaemia, vomiting, upperrespiratory tract infection, nausea, cough, fungal skin infection, peripheral oedema and vomiting.

Initial Combination Therapy with Metformin:

Diarrhea, dyspepsia, flatulence, vomiting and headache.

Initial Combination Therapy with PPARγ agonist:

Asymptomatic decreased blood glucose and symptomatic hypoglycaemia

4.10 Overdoses:

During controlled clinical trials in healthy subjects, single doses of up to 800 mg Sitagliptin were generally well tolerated. 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 haemodialysis session. Prolonged

haemodialysis may be considered if clinically appropriate. It is not known if Sitagliptin is dialysable by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

ATC classification

Pharmacotherapeutic group: Drugs used in diabetes, Dipeptidyl peptidase 4 (DPP-4) inhibitors

ATC code: A10BH01

Sita is a member of a class of oral anti-hyperglycaemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors. The improvement in glycaemic 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 hypoglycaemia. 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 hyperglycaemia, these changes in insulin and glucagon levels lead to lower haemoglobin A1c (HbA1c) and lower fasting and postprandial glucose concentrations. The glucose-dependent mechanism of Sitagliptin is distinct from the mechanism of sulphonylureas, which increase insulin secretion even when glucose levels are low and can lead to hypoglycaemia 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.

5.2 Pharmacokinetic properties

Retention time

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 Sita had no effect on the pharmacokinetics, Sita 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 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 administration of an oral [14C] Sitagliptin dose to healthy subjects, approximately 100 % of the administered radioactivity was eliminated in faeces (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.

Characteristics in patients

The pharmacokinetics of Sitagliptin was generally similar in healthy subjects and in patients with type 2 diabetes.

Renal impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of a reduced dose of Sitagliptin (50-mg) in patients with varying degrees of chronic renal impairment compared to normal healthy control subjects. The study included patients with renal impairment classified on the basis of creatinine clearance as mild (50 to < 80 ml/min), moderate (30 to < 50 ml/min), and severe (< 30 ml/min), as well as patients with end-stage renal disease (ESRD) on haemodialysis.

Patients with mild renal impairment did not have a clinically meaningful increase in the plasma concentration of Sitagliptin as compared to normal healthy control subjects. An approximately 2-fold increase in the plasma AUC of Sitagliptin was observed in patients with moderate renal impairment, and an approximately 4-fold increase was observed in patients with severe renal impairment and in patients with ESRD on haemodialysis, as compared to normal healthy control subjects. Sitagliptin was modestly removed by haemodialysis (13.5 % over a 3- to 4-hour haemodialysis 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 moderate and severe renal impairment, as well as in ESRD patients requiring dialysis.

Hepatic impairment

No dose adjustment for Sita is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score ≤ 9). There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score > 9). However, because Sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetics of Sitagliptin.

Elderly

No dose 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.

Paediatric

No studies with Sita have been performed in pediatric patients.

Other patient characteristics

No dose adjustment is necessary based on gender, race, or body mass index (BMI). These characteristics had no clinically meaningful effect on the pharmacokinetics of Sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

5.3 Pre-clinical safety data

Renal and liver toxicity were observed in rodents at systemic exposure values 58 times the human exposure level, while the no-effect level was found at 19 times the human exposure level. Incisor teeth abnormalities were observed in rats at exposure levels 67 times the clinical exposure level; the no-effect level for this finding was 58-fold based on the 14-week rat study. The relevance of these findings for humans is unknown. Transient treatment-related physical signs, some of which suggest neural toxicity, such as open-mouth breathing, salivation, white foamy emesis, ataxia, trembling, decreased activity, and/or hunched posture were observed in dogs at exposure levels approximately 23 times the clinical exposure level. In addition, very slight to slight skeletal muscle degeneration was also observed histologically at doses resulting in systemic exposure levels of approximately 23 times the human exposure level. A no-effect level for these findings was found at an exposure 6-fold the clinical exposure level.

Sitagliptin has not been demonstrated to be genotoxic in preclinical studies. Sitagliptin was not carcinogenic in mice. In rats, there was an increased incidence of hepatic adenomas and carcinomas at systemic exposure levels 58 times the human exposure level. Since hepatotoxicity has been shown to correlate with induction of hepatic neoplasia in rats, this increased incidence of hepatic tumours in rats was likely secondary to chronic hepatic toxicity at this high dose. Because of the high safety margin (19-fold at this no-effect level), these neoplastic changes are not considered relevant for the situation in humans.
No adverse effects upon fertility were observed in male and female rats given Sitagliptin prior to and throughout mating.

In a pre-/postnatal development study performed in rats Sitagliptin showed no adverse effects.

Reproductive toxicity studies showed a slight treatment-related increased incidence of fetal rib malformations (absent, hypoplastic and wavy ribs) in the offspring of rats at systemic exposure levels more than 29 times the human exposure levels. Maternal toxicity was seen in rabbits at more than 29 times the human exposure levels. Because of the high safety margins, these findings do not suggest a relevant risk for human reproduction. Sitagliptin is secreted in considerable amounts into the milk of lactating rats (milk/plasma ratio: 4:1).

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

For Core:

- Dicalcium phosphate
- Croscarmellose Sodium
- Kollidon K-30
- Magnesium Stearate
- Avicel pH 102
- Isopropyl Alcohol
- Aerosil 200

Film coating ingredients:

- Opashine pearl orange S 13000-C 4000
- Methanol
- Eudragit E 100
- Methylene Chloride
- Isopropyl Alcohol
- Polyethylene Glycol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

2 years

6.4 Special Precautions for Storage

- Stored at or below 30ºC.
- Protect from heat sunlight and moisture
- Keep away from heat, moisture, light and children

6.5 Nature and Contents of Container

4 x 7's tablets packed in Alu-Alu blister, in bleach board unit carton with leaflet.

6.6 Special Precautions for Disposal and other Handling

Not applicable

7. Marketing Authorization Holder and Manufacturing Site Address

Name: CCL Pharmaceuticals (Pvt.) Ltd.
Address: 62-Industrial Estate, Kot Lakhpat, Lahore-54770, Pakistan.
Telephone: +92-42-5114753
Fax: +92-42-35114382
E-mail: mail.ccl@cclpharma.com,

8. Marketing Authorization Number

055329

9. Date of First Authorization / Renewal of Authorization

Date of first authorization	27-02-2009
Date of second renewal	27-02-2014
Date of third renewal	27-02-2019
Date of last renewal	27-02-2024
Date of next renewal	27-02-2029

10. Date of Revision Of The Text

27-02-2029