For use in India only

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Sitagliptin Tablets IP 25 mg, 50 mg and 100 mg

MSN SITA 25, 50 & 100
एम एस एन सीटा २५,५०&१००

To be sold by retail on the prescription of Registered Medicinal Practitioner only

PRESCRIBING INFORMATION

1. GENERIC NAME
Sitagliptin Tablets IP 25 mg, 50 mg and 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Sitagliptin Tablets 25 mg
Each Film Coated Tablet Contains
Sitagliptin Phosphate Monohydrate IP
Equivalent to Sitagliptin 25 mg
Colours: Titanium Dioxide IP
Ferric Oxide Yellow USP-NF
Ferric Oxide Red USP-NF

Sitagliptin Tablets 50 mg
Each Film Coated Tablet Contains
Sitagliptin Phosphate Monohydrate IP
Equivalent to Sitagliptin 50 mg
Colours: Titanium Dioxide IP
Ferric Oxide Yellow USP-NF
Ferric Oxide Red USP-NF

Sitagliptin Tablets 100 mg
Each Film Coated Tablet Contains
Sitagliptin Phosphate Monohydrate IP
Equivalent to Sitagliptin 100 mg
Colours: Titanium Dioxide IP
Ferric Oxide Yellow USP-NF
Ferric Oxide Red USP-NF

3. DOSAGE FORM AND STRENGTH
Tablets; 25 mg, 50 mg and 100 mg

4. CLINICAL PARTICULARS
4.1. Indications
- Sitagliptin is indicated as adjunct to diet and exercise to improve glycemic control in patients with type-II diabetes.
- Use of Sitagliptin Phosphate in combination with Metformin and a PPARγ agonist 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.

4.2. Posology and Method of Administration
Posology
The dose is 100 mg sitagliptin once daily. When used in combination with metformin and/or a PPARγ agonist, the dose of metformin and/or PPARγ agonist should be maintained, and Sitagliptin 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.

Renal impairment
When considering the use of Sitagliptin in combination with another anti-diabetic medicinal product, its conditions for use in patients with renal impairment should be checked.
- For patients with mild renal impairment (glomerular filtration rate [GFR] ≥ 60 to < 90 mL/min), no dose adjustment is required.
- For patients with moderate renal impairment (GFR ≥ 45 to < 60 mL/min), no dosage adjustment is required.
- For patients with moderate renal impairment (GFR ≥ 30 to < 45 mL/min), the dose of Sitagliptin is 50 mg once daily.
- For patients with severe renal impairment (GFR ≥ 15 to <30 mL/min) or with end-stage renal disease (ESRD) (GFR < 15 mL/min), including those requiring haemodialysis or peritoneal dialysis, the dose of Sitagliptin is 25 mg once daily.

Treatment may be administered without regard to the timing of dialysis. Because there is a dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of Sitagliptin and periodically thereafter.

Hepatic impairment
No dose adjustment is necessary for patients with mild to moderate hepatic impairment. However, because Sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetics of Sitagliptin.

Method of Administration
Sitagliptin can be taken with or without food.

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

4.4. Special Warnings and Precautions for Use
General
Sitagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Acute pancreatitis
Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of sitagliptin (with or without supportive treatment), but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, Sitagliptin and other potentially suspect medicinal products should be discontinued; if acute pancreatitis is confirmed, Sitagliptin should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Hypoglycaemia when used in combination with other anti-hyperglycaemic medicinal products
In clinical trials of Sitagliptin 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. Hypoglycaemia has been observed when sitagliptin was used in combination with insulin or a sulphonylurea. Therefore, to reduce the risk of hypoglycaemia, a lower dose of sulphonylurea or insulin may be considered.

Renal impairment
Sitagliptin is renally excreted. To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with GFR < 45 mL/min, as well as in ESRD patients requiring haemodialysis or peritoneal dialysis. When considering the use of sitagliptin in combination with another anti-diabetic medicinal product, its conditions for use in patients with renal impairment should be checked.

Hypersensitivity reactions
Post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin have been reported. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, Sitagliptin should be discontinued. Other potential causes for the event should be assessed, and alternative treatment for diabetes initiated.

Bullous pemphigoid
There have been post-marketing reports of bullous pemphigoid in patients taking DPP-4 inhibitors including sitagliptin. If bullous pemphigoid is suspected, Sitagliptin should be discontinued.

4.5. Drug Interactions
Effects of other medicinal products on Sitagliptin
Clinical data described below suggest that the risk for clinically meaningful interactions by co-administered medicinal products is low. In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin is CYP3A4, with contribution from CYP2C8. In patients with normal renal function, metabolism, including via CYP3A4, plays only a small role in the clearance of sitagliptin. Metabolism may play a more significant role in the elimination of sitagliptin in the setting of severe renal impairment or end-stage renal disease (ESRD). For this reason, it is possible that potent CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the pharmacokinetics of sitagliptin in patients with severe renal impairment or ESRD. The effect of potent CYP3A4 inhibitors in the setting of renal impairment has not been assessed in a clinical study. In vitro transport studies showed that sitagliptin is a substrate for p-glycoprotein and organic anion transporter-3 (OAT3). OAT3 mediated transport of sitagliptin was inhibited in vitro by probenecid, although the risk of clinically meaningful interactions is considered to be low. Concomitant administration of OAT3 inhibitors has not been evaluated in vivo.

Metformin: Co-administration of multiple twice-daily doses of 1,000 mg metformin with 50 mg sitagliptin did not meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.

Ciclosporin: A study was conducted to assess the effect of ciclosporin, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Co-administration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of ciclosporin increased the AUC and Cmax of sitagliptin by approximately 29 % and 68 %, respectively. These changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of Sitagliptin was not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

Effects of sitagliptin on other medicinal products
Digoxin: Sitagliptin had a small effect on plasma digoxin concentrations. Following administration of 0.25 mg digoxin concomitantly with 100 mg of sitagliptin daily for 10 days, the plasma AUC of digoxin was increased on average by 11 %, and the plasma Cmax on average by 18 %. No dose adjustment of digoxin is recommended. However, patients at risk of digoxin toxicity should be monitored for this when sitagliptin and digoxin are administered concomitantly.

In vitro data suggest that sitagliptin does not inhibit nor induce CYP450 isoenzymes. In clinical studies, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing in vivo evidence of a low propensity for causing interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT). Sitagliptin may be a mild inhibitor of p-glycoprotein in vivo.

4.6. Use in Special Populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)
Pregnancy
There are no adequate data from the use of Sitagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses. The potential risk for humans is unknown. Due to lack of human data, Sitagliptin should not be used during pregnancy.

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

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

Pediatric Use
The safety and effectiveness of Sitagliptin have not been established in pediatric patients.

Geriatric Use
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. Because sitagliptin is substantially excreted by the kidney, and because aging can be associated with reduced renal function, renal function should be assessed more frequently in elderly patients.

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 m^2
(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
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).

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

Adverse reaction	Frequency of adverse reaction
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 4.4.

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. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ To report a side effect. You can also report side effects directly via the National Pharmacovigilance Programme of India by calling on 1800 180 3024 or you can report to MSN Labs on +91- 40 38265227 (Direct line); +91 7331134745 (WhatsApp). By reporting side effects, you can help provide more information on the safety of this product.

4.9. Overdose
During controlled clinical trials in healthy subjects, single doses of up to 800 mg Sitagliptin were administered. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg Sitagliptin.

In the event of an overdose, it is reasonable to employ supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy as dictated 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
Pharmacotherapeutic group: Drugs used in diabetes, Dipeptidyl peptidase 4 (DPP-4) inhibitors, ATC code: A10BH01.

5.1. Mechanism of action
Sitagliptin 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 signalling 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
Absorption
Following 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, mean plasma AUC of sitagliptin was 8.52 μM•hr, C_{max} was 950 nM. The absolute bioavailability of sitagliptin is approximately 87 %. Since co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, Sitagliptin may be administered with or without food.

Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for C_{max} and C_{24hr} (C_{max} increased in a greater than dose-proportional manner and C_{24hr} 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 [^{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. 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 [^{14}C] 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 $t_{1/2}$ 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 pglycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, ciclosporin, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin. Sitagliptin is not a substrate for OCT2 or OAT1 or $PEPT_{1/2}$ 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 were 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 mild, moderate, and severe renal impairment, as well as patients with ESRD on haemodialysis. 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 (GFR ≥ 60 to < 90 mL/min) and patients with moderate renal impairment (GFR ≥ 45 to < 60 mL/min), 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 (GFR ≥ 30 to < 45 mL/min), and approximately 4-fold in patients with severe renal impairment (GFR < 30 mL/min), including in patients with ESRD on haemodialysis. 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 GFR < 45 mL/min.

Hepatic impairment
No dose adjustment for Sitagliptin 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 population
The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in paediatric patients (10 to 17 years of age) with type 2 diabetes. In this population, the dose-adjusted AUC of sitagliptin in plasma was approximately 18 % lower compared to adult patients with type 2 diabetes for a 100 mg dose. This is not considered to be a clinically meaningful difference compared to adult patients based on the flat PK/PD relationship between the dose of 50 mg and 100 mg. No studies with sitagliptin have been performed in paediatric patients with age <10 years.

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. Pharmacodynamic Properties
Clinical efficacy and safety
Overall, sitagliptin improved glycaemic control when used as monotherapy or in combination treatment in adult patients with type 2 diabetes.

Two studies were conducted to evaluate the efficacy and safety of sitagliptin monotherapy. Treatment with sitagliptin at 100 mg once daily as monotherapy provided significant improvements in HbA1c, fasting plasma glucose (FPG), and 2- hour post-prandial glucose (2-hour PPG), compared to placebo in two studies, one of 18- and one of 24-weeks duration. Improvement of surrogate markers of beta cell function, including HOMA-β (Homeostasis Model Assessment-β), proinsulin to insulin ratio, and measures of beta cell responsiveness from the frequently-sampled meal tolerance test were observed. The observed incidence of hypoglycaemia in patients treated with sitagliptin was similar to placebo. Body weight did not increase from baseline with sitagliptin therapy in either study, compared to a small reduction in patients given placebo.

The TECOS was a randomised study in 14,671 patients in the intention-to-treat population with an HbA1c of ≥ 6.5 to 8.0 % with established CV disease who received sitagliptin (7,332) 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and < 50 mL/min/1.73 m^2) or placebo (7,339) added to usual care targeting regional standards for HbA1c and CV risk factors. Patients with an eGFR < 30 mL/min/1.73 m^2 were not to be enrolled in the study. The study population included 2,004 patients ≥ 75 years of age and 3,324 patients with renal impairment (eGFR < 60 mL/min/1.73 m^2). Over the course of the study, the overall estimated mean (SD) difference in HbA1c between the sitagliptin and placebo groups was 0.29 % (0.01), 95 % CI (-0.32, -0.27); p < 0.001.

After a median follow up of 3 years, sitagliptin, when added to usual care, did not increase the risk of major adverse cardiovascular events or the risk of hospitalisation for heart failure compared to usual care without sitagliptin in patients with type 2 diabetes.

Paediatric population
A 54-week, double-blind study was conducted to evaluate the efficacy and safety of sitagliptin 100 mg once daily in paediatric patients (10 to 17 years of age) with type 2 diabetes who were not on anti-hyperglycaemic therapy for at least 12 weeks (with HbA1c 6.5% to 10%) or were on a stable dose of insulin for at least 12 weeks (with HbA1c 7% to 10%). Patients were randomised to sitagliptin 100 mg once daily or placebo for 20 weeks. Mean baseline HbA1c was 7.5%. Treatment with sitagliptin 100 mg did not provide significant improvement in HbA1c at 20 weeks. The reduction in HbA1c in patients treated with Sitagliptin (N=95) was 0.0% compared to 0.2% in patients treated with placebo (N=95), a difference of -0.2% (95% CI: -0.7, 0.3).

6. NONCLINICAL PROPERTIES
6.1. 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. PHARMACEUTICAL PARTICULARS
7.1. Incompatibilities
Not applicable.

7.2. Packing Information
10's Blister pack.

7.3. Storage and Handling Information
Do not store above 30˚C.

KEEP OUT OF REACH FOR CHILDREN

8. PATIENT COUNSELING INFORMATION
Advise the patient to read the patient labelling (Patient Information).

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.

9. DETAILS OF MANUFACTURER
MSN Laboratories Private Limited,
Mekaguda, Telangana-509 228,
INDIA.

10. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE
TS/RR/2020-65026, 28/08/2020

11. DATE OF REVISION
May 2022

4030024-00