Prescribing Information (SUMMARY OF PRODUCT CHARACTERISTICS)

1. Name of the Finished Pharmaceutical Product
Sita-Met 50/500mg Tablet

2. Qualitative and Quantitative Composition

Each film coated tablet contains:
Sitagliptin (as Phosphate Monohydrate).....50mg
Metformin HCl.....500mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form
Pharmaceutical form: Tablets

Description: Orange pink capsular film coated tablets, plain on both sides.

4. Clinical Particulars:

4.1 Therapeutic Indications

For adult patients with type 2 diabetes mellitus:

Sita-Met is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin.
Sita-Met is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.

Sita-Met is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist.

Sita-Met is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control.

4.2 Posology and Method of Administration
The dose of antihyperglycaemic therapy with Sita-Met should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg Sitagliptin.

For patients inadequately controlled on maximal tolerated dose of Metformin monotherapy
For patients not adequately controlled on Metformin alone, the usual starting dose of Sita-Met should provide Sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) plus the dose of Metformin already being taken.

For patients switching from co-administration of Sitagliptin and Metformin
For patients switching from co-administration of Sitagliptin and Metformin, Sita-Met should be initiated at the dose of Sitagliptin and Metformin already being taken.

For patients inadequately controlled on dual combination therapy with the maximal tolerated dose of Metformin and a sulphonylurea
The dose of Sita-Met should provide Sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of Metformin similar to the dose already being taken. When Sita-Met is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be required to reduce the risk of hypoglycaemia.

For patients inadequately controlled on dual combination therapy with the maximal tolerated dose of Metformin and a PPARγ agonist
The dose of Sita-Met should provide Sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of Metformin similar to the dose already being taken.

For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of Metformin
The dose of Sita-Met should provide Sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of Metformin similar to the dose already being taken. When Sita-Met is used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycaemia.

For the different doses on Metformin, Sita-Met is available in strengths of 50 mg Sitagliptin and 850 mg Metformin hydrochloride or 1,000 mg Metformin hydrochloride.

All patients should continue their diet with an adequate distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.

Special populations

Renal impairment:
Sita-Met should not be used in patients with moderate or severe renal impairment (creatinine clearance < 60 ml/min).

Hepatic impairment:
Sita-Met should not be used in patients with hepatic impairment.

Elderly:
As Metformin and Sitagliptin are excreted by the kidney, Sita-Met should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of Metformin-associated lactic acidosis, particularly in the elderly. Limited safety data on Sitagliptin is available in patients > 75 years of age and care should be exercised.

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

4.3 Method of Administration
Sita-Met should be given twice daily with meals to reduce the gastrointestinal undesirable effects associated with Metformin

4.4 Contra Indications
- Sita-Met is contraindicated in patients with:
- hypersensitivity to the active substances or to any of the excipients listed in formulation
- diabetic ketoacidosis, diabetic pre-coma
- moderate and severe renal impairment (creatinine clearance < 60 mL/min)
- acute conditions with the potential to alter renal function such as:
  - dehydration,
  - severe infection
  - shock,
  - intravascular administration of iodinated contrast agents
- acute or chronic disease which may cause tissue hypoxia such as:
  - cardiac or respiratory failure
  - recent myocardial infarction
  - shock
- hepatic impairment
- acute alcohol intoxication, alcoholism
- Breast-feeding.

4.5 Special Warning and Precautions for Use

General
Sita-Met should not be used in patients with type 1 diabetes and must not be used 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-Met and other potentially suspect medicinal products should be discontinued.

Lactic acidosis:
Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to Metformin accumulation. Reported cases of lactic acidosis in patients on Metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any conditions associated with hypoxia.

Diagnosis
Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate
levels above 5 mmol/l, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient hospitalised immediately.

Renal function:
Metformin and Sitagliptin are known to be substantially excreted by the kidney. Metformin-related lactic acidosis increases with the degree of impairment of renal function; therefore, serum creatinine concentrations should be determined regularly:

- at least once a year in patients with normal renal function
- at least two to four times a year in patients with serum creatinine levels at or above the upper limit of normal and in elderly patients.

Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive or diuretic therapy or when starting treatment with a non-steroidal anti-inflammatory drug (NSAID).

Hypoglycaemia:
Patients receiving Sita-Met in combination with a sulphonylurea or with insulin may be at risk for hypoglycaemia. Therefore, a reduction in the dose of the sulphonylurea or insulin may be necessary.

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 three months after initiation of treatment with Sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue Sita-Met, assess for other potential causes of the event, and institute alternative treatment for diabetes.

Surgery:
As Sita-Met contains Metformin hydrochloride, the treatment should be discontinued 48 hours before elective surgery with general, spinal or epidural anaesthesia. Sita-Met should not usually be resumed earlier than 48 hours afterwards and only after renal function has been re-evaluated and found to be normal.

Administration of iodinated contrast agent:
The intravascular administration of iodinated contrast agents in radiological studies can lead to renal failure which has been associated with lactic acidosis in patients receiving Metformin. Therefore, Sita-Met should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Change in clinical status of patients with previously controlled type 2 diabetes:
A patient with type 2 diabetes previously well controlled on Sita-Met who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and Metformin levels. If acidosis of either form occurs, Sita-Met must be stopped immediately and other appropriate corrective measures initiated.

4.6 Interaction with other Medicinal Products and other forms of Interactions

Co-administration of multiple doses of Sitagliptin (50 mg twice daily) and Metformin (1,000 mg twice daily) did not meaningfully alter the pharmacokinetics of either Sitagliptin or Metformin in patients with type 2 diabetes. Pharmacokinetic drug interaction studies with Sita-Met have not been performed; however, such studies have been conducted with the individual active substances of Sita-Met, Sitagliptin and Metformin. There is increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic insufficiency) due to the Metformin active substance of Sita-Met. Consumption of alcohol and medicinal products containing alcohol should be avoided.

Cationic medicinal products that are eliminated by renal tubular secretion (e.g., cimetidine) may interact with Metformin by competing for common renal tubular transport systems. A study conducted in seven normal healthy volunteers showed that cimetidine, administered as 400 mg twice daily, increased Metformin systemic exposure (AUC) by 50% and C_{max} by 81 %. Therefore, close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are co-administered.

The intravascular administration of iodinated contrast agents in radiological studies may lead to renal failure, resulting in Metformin accumulation and a risk of lactic acidosis. Therefore, Sita-Met should be discontinued prior to, or at the time of the

test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Combination requiring precautions for use:
Glucocorticoids (given by systemic and local routes) beta-2-agonists and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment with such medicinal products. If necessary, the dose of the anti-hyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

ACE-inhibitors may decrease the blood glucose levels. If necessary, the dose of the antihyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

Effects of other medicinal products on Sitagliptin:
Clinical data described below suggest that the risk for clinically meaningful interactions following co-administration of other medicinal products is low.

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 C_{max} 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.

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 phamacokinetics of Sitagliptin in patients with severe renal impairment or ESRD. The effects 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.

Effects of Sitagliptin on other medicinal products:
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 had a small effect on plasma digoxin concentrations, and may be a mild inhibitor of p-glycoprotein in vivo. 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 C_{max} 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.

4.7 Additional Information on Special Populations

Not Applicable

4.8 Fertility, Pregnancy and Lactation

Pregnancy:
There are no adequate data from the use of Sitagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses of Sitagliptin.

A limited amount of data suggests the use of Metformin in pregnant women is not associated with an increased risk of congenital malformations. Animal studies with Metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development.

Sita-Met should not be used during pregnancy. If a patient wishes to become pregnant or if a pregnancy occurs, treatment with Sita-Met should be discontinued and switched to insulin treatment as soon as possible.

Breast-feeding:
No studies in lactating animals have been conducted with the combined active substances of Sita-Met. In studies performed with the individual active substances, both Sitagliptin and Metformin are excreted in the milk of lactating rats. Metformin is excreted in human milk in small amounts. It is not known whether Sitagliptin is excreted in human milk. Sita-Met must therefore not be used in women who are breast-feeding.

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

4.9 Effects on Ability to Drive and Use Machines: Not Known

4.10 Undesirable Effects

There have been no therapeutic clinical trials conducted with Sita-Met tablets. Serious adverse reactions including pancreatitis and hypersensitivity reactions have been reported. Hypoglycemia has been reported in combination with sulphonylurea (13.8%) and insulin (10.9%).

Sitagliptin and Metformin
Tabulated list of adverse reactions
Adverse reactions are listed below as MedDRA preferred term by system organ class and absolute frequency (Table 1). 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 and post marketing experience

Adverse reaction	**Frequency of adverse reaction by treatment regimen**			
	Sitagliptin with Metformin	**Sitagliptin with Metformin and a Sulphonylurea**	**Sitagliptin with Metformin and a PPARγ Agent (rosiglitazone)**	**Sitagliptin with Metformin and Insulin**
Time-point	**24-week**	**24-week**	**18-week**	**24-week**
Infections and infestations				
Upper respiratory tract infection			Common‡	
fungal skin infection			Uncommon‡	
Immune system disorders				
hypersensitivity reactions including anaphylactic responses *, †	Frequency not known			
Metabolism and nutrition disorders				
hypoglycaemia†	Common	Very common	Common	Very common

Nervous system disorders				
headache			Common	Uncommon
somnolence	Uncommon			
Respiratory, thoracic and mediastinal disorders				
cough			Common‡	
interstitial lung disease*	Frequency not known			
Gastrointestinal disorders				
diarrhoea	Uncommon		Common	
nausea	Common			
flatulence	Common			
constipation	Uncommon	Common		
upper abdominal pain	Uncommon			
vomiting	Common	Frequency not known *	Common	Frequency not known*
dry mouth				Uncommon
acute pancreatitis *, †	Frequency not known			
fatal and non-fatal haemorrhagic and necrotizing pancreatitis*, †	Frequency not known			
Skin and subcutaneous tissue disorders				
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			

Musculoskeletal and connective tissue disorders				
arthralgia*	Frequency not known			
myalgia*	Frequency not known			
pain in extremity*	Frequency not known			
back pain*	Frequency not known			
Renal and urinary disorders				
impaired renal function*	Frequency not known			
acute renal failure*	Frequency not known			
General disorders and administration site conditions				
peripheral oedema			Common‡	
Investigations				
blood glucose decreased	Uncommon			

‡54-week time point.
*Adverse reactions were identified through postmarketing surveillance.
Additional information on the individual active substances of the fixed dose combination

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 providers are asked to report any suspected adverse reactions to the marketing authorization holder or if available via the national reporting system (See details below);

Paper based reporting: TMDA yellow card
Online reporting: https://sqrt.tmda.go.tz/
*USSD reporting: send a simple short text message to report any suspected Adverse Drug Reaction by dialing *152*00# and follow the instructions*.

4.11 Overdoses:

No data are available with regard to overdose of Sita-Met.

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.

A large overdose of Metformin (or co-existing risks of lactic acidosis) may lead to lactic acidosis which is a medical emergency and must be treated in hospital. The most effective method to remove lactate and Metformin is haemodialysis.

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.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastro-intestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

5. Pharmacological Properties

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group:
Drugs used in diabetes, combinations of oral blood Glucose lowering drugs

ATC code:
A10BD07

Sita-Met combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: Sitagliptin phosphate, a dipeptidyl peptidase 4 (DPP-4) inhibitor and Metformin hydrochloride, a member of the biguanide class.

Sitagliptin
Mechanism of action:
Sitagliptin phosphate is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzymes for the treatment of type 2 diabetes. The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, Sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). 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. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. When blood glucose levels are low, insulin release is not enhanced and glucagon secretion is not suppressed. 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. Sitagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulphonylureas or meglitinides, biguanides, peroxisome proliferator-activated receptor gamma (PPARγ) agonists, alpha-glucosidase inhibitors, and amylin analogues.

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.

Clinical efficacy and safety
Overall, Sitagliptin improved glycaemic control when used as monotherapy or in combination treatment. In clinical trials, Sitagliptin as monotherapy improved glycaemic control with significant reductions in haemoglobin A_{1c} (HbA_{1c}) 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-β), proinsulin to insulin ratio, and measures of beta cell responsiveness from the frequently-sampled meal tolerance test were observed.

Studies of Sitagliptin in combination with Metformin:
In a 24-week, placebo-controlled clinical study to evaluate the efficacy and safety of the addition of Sitagliptin 100 mg once daily to ongoing Metformin, Sitagliptin provided significant improvements in glycaemic parameters compared with placebo. Change from baseline in body weight was similar for patients treated with Sitagliptin relative to placebo. In this study there was a similar incidence of hypoglycaemia reported for patients treated with Sitagliptin or placebo.

In a 24-week placebo-controlled factorial study of initial therapy, Sitagliptin 50 mg twice daily in combination with Metformin (500 mg or 1,000 mg twice daily) provided significant improvements in glycaemic parameters compared with either monotherapy. The decrease in body weight with the combination of Sitagliptin and Metformin was similar to that observed with Metformin alone or placebo; there was no change from baseline for patients on Sitagliptin alone. The incidence of hypoglycaemia was similar across treatment groups.

Study of Sitagliptin in combination with Metformin and a sulphonylurea:
A 24-week placebo-controlled study was designed to evaluate the efficacy and safety of Sitagliptin (100 mg once daily) added to Glimepiride (alone or in combination with Metformin). The addition of Sitagliptin to Glimepiride and Metformin provided significant improvements in glycaemic parameters. Patients treated with Sitagliptin had a modest increase in body weight (+1.1 kg) compared to those given placebo.

Study of Sitagliptin in combination with Metformin and a PPARγ agonist
A 54-week placebo-controlled study was designed to evaluate the efficacy and safety of Sitagliptin (100 mg once daily) added to the combination of Rosiglitazone and Metformin. The addition of Sitagliptin to Rosiglitazone and Metformin provided significant improvements in glycaemic parameters at the primary time point of Week 18, with improvements sustained through the end of the study. Change from baseline in body weight was similar for patients treated with Sitagliptin relative to placebo (1.9 vs. 1.3 kg).

Study of Sitagliptin in combination with Metformin and insulin
A 24-week placebo-controlled study was designed to evaluate the efficacy and safety of Sitagliptin (100 mg once daily) added to insulin (at a stable dose for at least 10 weeks) with or without Metformin (at least 1,500 mg). In patients taking pre-mixed insulin, the mean daily dose was 70.9 U/day. In patients taking non-pre-mixed (intermediate/long-acting) insulin, the mean daily dose was 44.3 U/day. Data from the 73 % of patients who were taking Metformin are presented in Table 2. The addition of Sitagliptin to insulin provided significant improvements in glycaemic parameters. There was no meaningful change from baseline in body weight in either group.

Table 2: HbA_{1c} results in placebo-controlled combination therapy studies of Sitagliptin and Metformin*

Study	**Mean baseline HbA_{1c} (%)**	**Mean change from baseline HbA_{1c} (%)**	**Placebo-corrected mean change in HbA_{1c} (%) (95 % CI)**
Sitagliptin 100 mg once daily added to ongoing Metformin therapy[%] (N=453)	8.0	-0.7[†]	-0.7[†‡] (-0.8, -0.5)
Sitagliptin 100 mg once daily added to ongoing Glimepiride + Metformin therapy[%] (N=115)	8.3	-0.6[†]	-0.9[†‡] (-1.1, -0.7)
Sitagliptin 100 mg once daily added to ongoing rosiglitazone + Metformin therapy (N=170)			
Week 18	8.8	-1.0[†]	-0.7[†‡] (-0.9, -0.5)
Week 54	8.8	-1.0[†]	-0.8[†‡] (-1.0, -0.5)
Sitagliptin 100 mg once daily added to ongoing	8.7	-0.7[§]	-0.5[§,‡] (-0.7, -0.4)

insulin + Metformin therapy [%] (N=223)			
Initial Therapy (twice daily) [%]: Sitagliptin 50 mg + Metformin 500 mg (N=183)	8.8	-1.4[†]	-1.6[†‡] (-1.8, -1.3)
Initial Therapy (twice daily) [%]: Sitagliptin 50 mg + Metformin 1,000 mg (N=178)	8.8	-1.9[†]	-2.1[†‡] (-2.3, -1.8)

* All Patients Treated Population (an intention-to-treat analysis).
[†] Least squares mean adjusted for prior antihyperglycaemic therapy status and baseline value.
[‡] p< 0.001 compared to placebo or placebo + combination treatment.
[%] HbA_{1c} (%) at week 24
[§] Least squares mean adjusted for insulin use at Visit 1 (pre-mixed vs. non-pre-mixed [intermediate- or long-acting]), and baseline value.

In a 52-week study, comparing the efficacy and safety of the addition of Sitagliptin 100 mg once daily or glipizide (a sulphonylurea) in patients with inadequate glycaemic control on Metformin monotherapy, Sitagliptin was similar to glipizide in reducing HbA_{1c} (-0.7 % mean change from baselines at week 52, with baseline HbA_{1c} of approximately 7.5 % in both groups). The mean glipizide dose used in the comparator group was 10 mg per day with approximately 40% of patients requiring a glipizide dose of ≤ 5 mg/day throughout the study. However, more patients in the Sitagliptin group discontinued due to lack of efficacy than in the glipizide group. Patients treated with Sitagliptin exhibited a significant mean decrease from baseline in body weight (-1.5 kg) compared to a significant weight gain in patients administered glipizide (+1.1 kg). In this study, the proinsulin to insulin ratio, a marker of efficiency of insulin synthesis and release, improved with Sitagliptin and deteriorated with glipizide treatment. The incidence of hypoglycaemia in the Sitagliptin group (4.9 %) was significantly lower than that in the glipizide group (32.0 %).

Metformin

Mechanism of action
Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via three mechanisms:

- by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- in muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- By delaying intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

Clinical efficacy and safety

In humans, independently of its action on glycaemia, Metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: Metformin reduces total cholesterol, LDLc and triglyceride levels.

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with Metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the Metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p=0.0034

- a significant reduction of the absolute risk of any diabetes-related mortality: Metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p=0.017

- a significant reduction of the absolute risk of overall mortality: Metformin 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years, (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years (p=0.021)
  a significant reduction in the absolute risk of myocardial infarction: Metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years, (p=0.01).

Paediatric population

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

5.2 Pharmacokinetic Properties

Sitagliptin

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 8.52μM•hr, C_{max} was 950nM. 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 isoenzymes 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 $t_{½}$ 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, ciclosporin, 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 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 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 post-dose).

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
No studies with Sitagliptin have been performed in paediatric 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.

Metformin:

Absorption

After an oral dose of Metformin, tmax is reached in 2.5h. Absolute bioavailability of a 500 mg Metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, Metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of Metformin absorption is non-linear. At the usual Metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 µg/ml. In controlled clinical trials, maximum Metformin plasma levels (C_{max}) did not exceed 4 µg/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of Metformin. Following administration of a dose of 850 mg, a 40 % lower plasma peak concentration, a 25 % decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean Vd ranged between 63 – 276 l.

Biotransformation

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination

Renal clearance of Metformin is > 400 ml/min, indicating that Metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of Metformin in plasma.

5.3 Pre-Clinical Safety Data

No animal studies have been conducted with Sita-Met.

In 16-week studies in which dogs were treated with either metformin alone or a combination of metformin and sitagliptin, no additional toxicity was observed from the combination. The NOEL in these studies was observed at exposures to sitagliptin of approximately 6 times the human exposure and to metformin of approximately 2.5 times the human exposure.

The following data are findings in studies performed with sitagliptin or metformin individually.

Sitagliptin
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 treatment related effects on fertility were observed in male and female rats given sitagliptin prior to and throughout mating.

In a pre-/post-natal development study performed in rats sitagliptin showed no adverse effects.

Reproductive toxicity studies showed a slight treatment-related increased incidence of foetal 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).

Metformin
Preclinical data for metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6.1 Pharmaceutical Particulars

6.2 List of Excipients:

- Croscarmellose Sodium

- Avicel pH 102
- Kollidon K 30
- Magnesium Stearate
- Dicalcium Phosphate
- Aqua Shine Orange Pink
- Opadry Clear OY-S 29019

6.3 Incompatibilities
Not applicable.

6.4 Shelf-Life
2 years

6.5 Special Precautions for Storage
- Store below 30°C.
- Protect from heat, sunlight and moisture.
- Keep away from children.

6.6 Nature and Contents of Container
2 x 7's tablets packed in Alu/PVC blister, in bleach board unit carton with leaflet.

6.7 Special Precautions for Disposal and other Handling
No special requirements for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Name of the Marketing Authorization Holder
CCL Pharmaceuticals (Pvt.) Ltd
62-Industrial Estate, Kot Lakhpat, Lahore-54770,
Pakistan.

8. Marketing Authorization Number
TAN 20 HM 0526

9. Date of First Authorization / Renewal of Authorization
18/11/2020

10. Date of Revision of the Text