Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Duvel plus 50 mg/500 mg film-coated tablets

2. Qualitative and quantitative composition

Each film-coated tablet contains sitagliptin phosphate monohydrate equivalent to 50 mg of sitagliptin and 500 mg of metformin hydrochloride

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet.

Oblong-shaped beige color tablet with break line on one side and plain on the other

4. Clinical particulars

4.1 Therapeutic indications

For adult patients with type 2 diabetes mellitus:

- Duvel plus is indicated as an adjunct to diet and exercise to improve glycemic 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.
- Duvel plus 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.
- Duvel plus is indicated as triple combination therapy with a peroxisome proliferator- activated receptor gamma (PPARy) 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 PPARy agonist.
- Duvel plus is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycemic control.

4.2 Posology and method of administration

Posology

The dosage of Duvel plus should be individualized on the basis of patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of l00mg sitagliptin and 2000mg metformin

For patients inadequately controlled on maximal tolerated dose of metformin monotherapy

For patients not adequately controlled on metformin alone, the usual starting dose of Duvel plus 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, Duvel plus 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

When Duvel plus is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be required to reduce the risk of hypoglycemia (see section 4.4).

For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin

When Duvel plus is used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycemia (see section 4.4).

All patients should continue their recommended diet with an adequate distribution of carbohydrate intake during the day.

Special populations

Renal impairment

Duvel plus should not be used in patients with moderate or severe renal impairment (Creatinine clearance <60ml/min).

Hepatic impairment

Duvel plus should not be used in patients with hepatic impairment (see section 5.2).

Elderly

As metformin and sitagliptin are excreted by the kidney, Duvel plus 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 (see sections 4.3 and 4.4). Limited safety data on sitagliptin is available in patients >75 years of age and care should be exercised.

Method of administration

Duvel plus should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal side effects due to metformin. Duvel plus must not be split or divided before swallowing.

4.3 Contraindications

Sitagliptin + Metformin is contraindicated in patients with:

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 (see sections 4.4 and 4.8);
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis);
- Diabetic pre-coma;
- Severe renal failure (GFR< 30 mL/min) (see section 4.4);
- Acute conditions with the potential to alter renal function such as:
    - dehydration,
    - severe infection,
    - shock,
    - intravascular administration of iodinated contrast agents (see section 4.4);
- 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.

4.4 Special warnings and precautions for use

General

Sitagliptin + Metformin should not be used in patients with type 1 diabetes and must not be used for the treatment of diabetic ketoacidosis.

Lactic Acidosis

Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication may occur due to metformin accumulation.

Pancreatitis

There may be acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin + metformin hydrochloride. After initiation of combination therapy, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, combination therapy should promptly be discontinued and appropriate management should be initiated.

Impaired Hepatic Function

Since impaired hepatic function may be associated with lactic acidosis, combination of sitagliptin and metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Assessment of Renal Function

Metformin and sitagliptin are known to be substantially excreted by the kidney. The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive combination of sitagliptin and metformin. In the elderly, sitagliptin and metformin combination should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging can be associated with reduced renal function.

Alcohol Intake

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving combination of sitagliptin and metformin.

Surgical Procedures

Use of sitagliptin and metformin should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Use with Medications Known to Cause Hypoglycemia

Patients receiving sitagliptin and metformin in combination with sulphonylurea or with insulin may be at risk for hypoglycemia. Therefore, a reduction in the dose of the sulphonylurea or insulin may be necessary. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking - adrenergic blocking drugs.

Hypoxic States

Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on sitagliptin and metformin therapy, the drug should be promptly discontinued.

Loss of Control of Blood Glucose

When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold sitagliptin and metformin combination and temporarily administer insulin. Combination of sitagliptin and metformin may be reinstituted after the acute episode is resolved.

Hypersensitivity Reactions

Serious hypersensitivity reactions in patients treated with sitagliptin may be observed, these reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens- Johnson syndrome. If a hypersensitivity reaction is suspected, discontinue combination of sitagliptin and

metformin, assess for other potential causes for the event, and institute alternative treatment for diabetes.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of multiple doses of sitagliptin (50 mg twice daily) and metformin (1,000 mg twice daily) is not known to meaningfully alter the pharmacokinetics of either sitagliptin or metformin in patients with type 2 diabetes.

Pharmacokinetic drug interaction with Sitagliptin + Metformin is not known.

Concomitant use not recommended
Alcohol

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases offasting, malnutrition or hepatic impairment.

Iodinated contrast agents

Sitagliptin + Metformin must be discontinued prior to or at the time of the imaging procedure andnot restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable. (See sections 4.3 & 4.4)

Combinations requiring precautions for use

Some medicinal products can adversely affect renal function, which may increase the risk of lactic acidosis, e.g., NSAIDs, including selective cyclooxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use. Close monitoring of glycemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when such products are co administered.

Glucocorticoids (given by systemic and local routes) beta-2-agonists, and diuretics have intrinsic hyperglycemic 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-hyperglycemic 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 anti- hyperglycemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

Effects of other medicinal products on sitagliptin

Known In vitro and clinical data described below suggested that the risk for clinically meaningful interactions following co-administration of other medicinal products is low.

Known 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 effects of potent CYP3A4 inhibitors in the setting of renal impairment have not been assessed in a clinical study.

Known 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 vifro* by probenecid, although the risk of clinically meaningful interactions is considered to be low. Concomitant administration of OAT3 inhibitors is not known to be evaluated *in vivo.*

Cyclosporine. A known study shows the effect of cyclosporine, 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 cyclosporine is known to increase the AUC and C+ 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 is known to be increased on average by 11 %, and the plasma Can 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.

Known In vitro data suggest that sitagliptin does not inhibit nor induce CYP450 isoenzymes. In known 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 Fertility, pregnancy, and lactation

Pregnancy

There are no adequate data from the use of sitagliptin in pregnant women. Known studies in animals have shown reproductive toxicity at high doses of sitagliptin (see section 5.3).

A limited amount of known 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 fetal development, parturition or postnatal development (see also section 5.3).

Sitagliptin + Metformin should not be used during pregnancy. If a patient wishes to become pregnant or if a pregnancy occurs, treatment should be discontinued and the patient switched to insulin treatment as soon as possible

Breast-feeding

No studies in lactating animals is known with the combined active substances of this medicinal product. Known 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. Sitagliptin + Metformin must therefore not be used in women who are breast-feeding (see section 4.3).

Fertility

Animal data is not known to suggest an effect of treatment with sitagliptin on male and female fertility. Human data are lacking.

4.7 Effects on ability to drive and use machines.

Rivaroxaban has minor influence on the ability to drive and use machines. Adverse reactions like syncope (frequency: uncommon) and dizziness (frequency: common) have been reported (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines

4.8 Undesirable effects

Reporting of suspected adverse reactions

Healthcare professionals are asked to report any suspected adverse reactions to the pharmacy and poisons board, through the Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

Summary of the safety profile

There have been no known therapeutic clinical trials conducted with Sitagliptin + Metformin tablets. Serious adverse reactions including pancreatitis and hypersensitivity reactions are known. Hypoglycemia are known to be 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 (ñ 1/10); common (ñ 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 known clinical studies of sitagliptin and metformin alone, 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	
hypoglycemia[†]	Common
Nervous system disorders	
somnolence	Uncommon

Respiratory, thoracic and mediastinal disorders	
interstitial lung disease*	Frequency not known
Gastrointestinal disorders	
diarrhea	Uncommon
nausea	Common
flatulence	Common
constipation	Uncommon
upper abdominal pain	Uncommon
vomiting	Common
acute pancreatitis [*,†,‡]	Frequency not known
fatal and non-fatal hemorrhagic 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
pain in extremity*	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

*Known post-marketing adverse reactions.
See section 4.4.
See *TECOS Cardiovascular Safety Study* below.

Description of selected adverse reactions

Some adverse reactions are known to be observed more frequently in studies of combination use of sitagliptin and metformin with other anti-diabetic medicinal products than in studies of sitagliptin and metformin alone. These included hypoglycemia (frequency very common with sulphonylurea or insulin), constipation (common with sulphonylurea),

peripheral edema (common with pioglitazone), and headache and dry mouth (uncommon with insulin).

Sitagliptin
In known monotherapy studies of sitagliptin 100 mg once daily alone compared to placebo, adverse reactions reported were headache, hypoglycemia, constipation, and dizziness.
Among these patients, adverse events reported regardless of causal relationship to medicinal product occurring in at least 5 % included upper respiratory tract infection and nasopharyngitis. In addition, osteoarthritis and pain in extremity were reported with frequency uncommon (> 0.5 % higher among sitagliptin users than that in the control group).

Metformin
Gastrointestinal symptoms are known to be reported very commonly in clinical studies and post- marketing use of metformin. Gastrointestinal symptoms such as nausea, vomiting, diarrhea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases. Additional adverse reactions associated with metformin include metallic taste (common); lactic acidosis, liver function disorders, hepatitis, urticaria, erythema, and pruritus (very rare). Long-term treatment with metformin are known to be associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B12 deficiency (e.g., megaloblastic anemia). Frequency categories are based on information available from metformin Summary of Product Characteristics available in the EU.

TECOS Cardiova.scular Safety Study
The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7,332 patients treated with sitagliptin, 100 mg daily (or 50 mg daily if the baseline eGFR was 30 and < 50 mL/min/1.73 m^2), and 7,339 patients treated with placebo in the intention-to-treat population. Both treatments were added to usual care targeting regional standards for HbAi and CV risk factors. The overall incidence of serious adverse events in patients receiving sitagliptin was similar to that in patients receiving placebo.
In the intention-to-treat population, among patients who were using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycemia was 2.7 % in sitagliptin-treated patients and 2.5
% in placebo-treated patients; among patients who were not using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycemia was 1.0 % in sitagliptin-treated patients and 0.7 % in placebo-treated patients. The incidence of adjudication-confirmed pancreatitis events was 0.3% in sitagliptin-treated patients and 0.2 % in placebo-treated patients.

4.9 Overdose

Known data from controlled clinical trials in healthy subjects, where single doses of up to 800 mg sitagliptin were administered, have shown minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. No data with doses above 800 mg is known. In Phase I multiple-dose known study data, no dose-related clinical adverse reactions are known 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 hemodialysis.
In known 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.
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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Combinations of oral blood glucose lowering drugs.

Sitagliptin + Metformin combines two anti-hyperglycemic medicinal products with complementary mechanisms of action to improve glycemic 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) enzyme 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 (PPARy) agonists, alpha-glucosidase inhibitors, and amylin analogues.
Data from a two-day known study in healthy subjects showed that 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 glycemic control when used as monotherapy or in combination
treatment.

In known clinical trials, sitagliptin as monotherapy improved glycemic control with significant reductions in hemoglobin Air (HbAi) and fasting and postprandial glucose. Reduction in fasting plasma glucose (FPG) was observed at 3 weeks, the first time point at which FPG was measured. The observed incidence of hypoglycemia 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-§ (Homeostasis Model Assessment-b), 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 known 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 glycemic 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 hypoglycemia reported for patients treated with sitagliptin or placebo.

In another known24-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 glycemic 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 hypoglycemia was similar across treatment groups.

Study of sitagliptin in combination with metformin and a sulphonylurea

A 24-week placebo-controlled study known 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 glycemic 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 PPARy agonist

A 26-week placebo-controlled study known to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to the combination of pioglitazone and metformin. The addition of sitagliptin to pioglitazone and metformin provided significant improvements in glycemic parameters. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo. The incidence of hypoglycemia was also similar in patients treated with sitagliptin or placebo.

Study of sitagliptin in combination with metformin and insulin

A 24-week placebo-controlled study known 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 is known to be 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 glycemic parameters. There was no meaningful change from baseline in body weight in either group.

Table 2: HbAi results from known placebo-controlled combination therapy studies of sitagliptin and metformin*

Data from Study	**Mean baseline** HbA« (%)	**Mean change frombaseline** HbAi (%)	**Placebo-corrected** mean **change in** HbAi‹ (%) (95 % CI)
Sitagliptin 100 mg once daily added to ongoing metformin therapy% (N=453)	8.0	-0.7J	-0.7 (-0.8, -0.5)
Sitagliptin 100 mg once daily added toongoing glimepiride + metformin therapy% (N'115)	8.3	-0.6$	-0.9 (-1.1, -0.7)
Sitagliptin 100 mg once daily added to ongoing pioglitazone + metformin therapy (N=152)	8.8	-1.2$	-0.7 (-1.0, -0.5)

Sitagliptin 100 mg once daily added toongoing insulin + metformin therapy % (N=223)	8.7	-0.7	-0.5 (-0.7, -0.4)
Initial Therapy (twice dai1y)%: Sitagliptin 50 mg + metformin 500 mg (N=183)	8.8	-1.4$	-1.6 (-1.8, -1.3)

Initial Therapy (twicedai1y)%: 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 means adjusted for prior anti-hyperglycemic therapy status and baseline value. pt 0.001 compared to placebo or placebo + combination treatment.
% HbAi (%) at week 24.

*HbAi (%) at week 26.

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 known study data, comparing the efficacy and safety of the addition of sitagliptin 100 mg once daily or glipizide (a sulphonylurea) in patients with inadequate glycemic control on metformin monotherapy, sitagliptin was similar to glipizide in reducing HbAi (-0.7 % mean change from baselines at week 52, with baseline HbAi 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 (+l.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 hypoglycemia in the sitagliptin group (4.9 %) was significantly lower than that in the glipizide group (32.0 %).

A 24-week placebo-controlled study involving 660 patients is known to evaluate the insulin- sparing efficacy and safety of sitagliptin (100 mg once daily) added to insulin glargine with orwithout metformin (at least 1,500 mg) during intensification of insulin therapy. Among patients taking metformin, baseline HbAi was 8.70 % and baseline insulin dose was 37 IU/day. Patients were instructed to titrate their insulin glargine dose based on finger stick fasting glucose values. Among patients taking metformin, at Week 24, the increase in daily insulin dose was 19 IU/day inpatients treated with sitagliptin and 24 IU/day in patients treated with placebo. The reduction in HbAi for patients treated with sitagliptin, metformin, and insulin was -1.35 % compared to -0.90
% for patients treated with placebo, metformin, and insulin, a difference of -0.45 % [95 % CI: - 0.62, -0.29]. The incidence of hypoglycemia was 24.9 % for patients treated with sitagliptin, metformin, and insulin and 37.8 % for patients treated with placebo, metformin, and insulin. The difference was mainly due to a higher percentage of patients in the placebo group experiencing 3 or more episodes of hypoglycemia (9.1 vs. 19.8 %). There was no difference in the incidence of severe hypoglycemia.

Metformin

Mechanism of action

Metformin is a biguanide with anti-hyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia.

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 utilization
- 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 favorable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term known clinical studies: metformin reduces total cholesterol, LDLc and triglyceride levels.

The known prospective randomized (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).

The TECOS was a randomized study in 14,671 patients in the intention-to-treat population with an HbAi 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 HbAi 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 HbAi between the sitagliptin and placebo groups was 0.29 % (0.01), 95 % CI (-0.32, -0.27); p < 0.001.

The primary cardiovascular endpoint was a composite of the first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina. Secondary cardiovascular endpoints included the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; first occurrence of the individual components of the primary composite; all-cause mortality; and hospital admissions for congestive heart failure.

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 hospitalization for heart failure compared to usual care without sitagliptin in patients with type 2 diabetes (Table 3).

Table 3: Rates of Composite Cardiovascular Outcomes and Key Secondary Outcomes

	Sitagliptin 100 mg		Placebo		Hazard Ratio (95% CI)	p-value†
	N (%)	Incidence rate per 100 patient-years*	N (%)	Incidence rate per 100 patient-years*		

Analysis in the Intention-to-Treat Population						
Number of patients	**7,332**		**7,339**		0.98 (0.89–1.08)	<0.001
Primary Composite Endpoint (Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina)	839 (11.4)	4.1	851 (11.6)	4.2		
Secondary Composite Endpoint (Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke)	745 (10.2)	3.6	746 (10.2)	3.6	0.99 (0.89–1.10)	<0.001
Secondary Outcome						
Cardiovascular death	380 (5.2)	1.7	366 (5.0)	1.7	1.03 (0.89-1.19)	0.711
All myocardial infarction (fatal and non-fatal)	300 (4.1)	1.4	316 (4.3)	1.5	0.95 (0.81–1.11)	0.487
All stroke (fatal and non-fatal)	178 (2.4)	0.8	183 (2.5)	0.9	0.97 (0.79–1.19)	0.760
Hospitalization for unstable angina	116 (1.6)	0.5	129 (1.8)	0.6	0.90 (0.70–1.16)	0.419
Death from any cause	547 (7.5)	2.5	537 (7.3)	2.5	1.01 (0.90–1.14)	0.875
Hospitalization for heart failure‡	228 (3.1)	1.1	229 (3.1)	1.1	1.00 (0.83–1.20)	0.983

* Incidence rate per 100 patient-years is calculated as 100 (total number of patients with > 1 event during eligible exposure period per total patient-years of follow-up).

Based on a Cox model stratified by region. For composite endpoints, the p-values correspond to a test of non-inferiority seeking to show that the hazard ratio is less than 1.3. For all other endpoints, the p-values correspond to a test of differences in hazard rates.

The analysis of hospitalization for heart failure was adjusted for a history of heart failure at baseline.

Pediatric population

There is no known data for use of Sitagliptin + Metformin in all subsets of the pediatric population in type 2 diabetes mellitus.

5.2 Pharmacokinetic properties

Sitagliptin + Metformin

A known bioequivalence study in healthy subjects shows that the sitagliptin/metformin hydrochloride combination tablets are bioequivalent to co-administration of sitagliptin phosphate and metformin hydrochloride as individual tablets.

The following statements reflect the pharmacokinetic properties of the individual active substances Sitagliptin + Metformin.

Sitagliptin

Absorption

Following oral administration of a 100-mg dose to healthy subjects, sitagliptin is known to be rapidly absorbed, with peak plasma concentrations (median Two) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin is known to be 8.52 pM•hr, Co was 950 nM. The absolute bioavailability of sitagliptin is known to be approximately 87 %. Since co-administration ofa high-fat meal with sitagliptin may not have any effect on the pharmacokinetics, sitagliptin may be administered with or without food.

Plasma AUC of sitagliptin is known to increase in a dose-proportional manner. Dose- proportionality is not known for Co and C24hr (C+ increased in a greater than dose-proportional manner and Cz4 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 known to be approximately 198 L. 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 may be excreted unchanged in the urine.

Known clinical data show that following a [' ^{4}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. Data from known *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8. This known data also showed that sitagliptin is not an inhibitor of CYP isoenzymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2Cl9 or 2B6, and is not an

inducer of CYP3A4 and CYP1A2.

Elimination

Known Scientific data has shown that following administration of an oral [^{14}C] sitagliptin dose to healthy subjects, approximately 100 % of the administered radioactivity is known to be eliminated in faeces (13 %) or urine (87 %) within one week of dosing. The apparent terminal t/, following a 100-mg oral dose of sitagliptin may approximately be 12.4 hours. Sitagliptin accumulates only minimally with multiple doses. The renal clearance is known to be 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 is not known. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin. Sitagliptin is not a substrate for OCT2 or OAT1 or PEPT1/2 transporters. *In vitro,* sitagliptin did not inhibit OAT3 (IC50=160 pM) or p-glycoprotein (up to 250 pM) mediated transport at therapeutically relevant plasma concentrations. In one known 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 may generally be similar in healthy subjects and in patients with type 2 diabetes.

Renal impairment

A single-dose, open-label study is known 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 hemodialysis. 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 is known to be 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 were not known to be clinically relevant, dosage adjustment in these patients may not be necessary.

Plasma AUC of sitagliptin may increase 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 patients with ESRD on hemodialysis. Sitagliptin is known to be modestly

removed by hemodialysis (13.5 % over a 3- to 4-hour hemodialysis 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 ñ 9). There is no clinical data known 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 may 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.

Pediatric

No studies with sitagliptin are known in pediatric patients.

Other patient characteristics

No dose adjustment is necessary based on gender, race, or body mass index (BMI). These characteristics may not have clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of known pharmacokinetic data.

Metformin

Absorption

After an oral dose of metformin, T+o is reached in 2.5 h. Absolute bioavailability of a 500 mg metformin tablet may approximately be 50-60 % in healthy subjects. After an oral dose, the non- absorbed fraction recovered in faeces may be 20-30 %.

After oral administration, metformin absorption may be saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is known to be non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are known to reach within 24-48 h and are generally less than 1 pg/mL. In known controlled clinical trials, maximum metformin plasma levels (C+) is not known to exceed 5 pg/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 is known to be 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 known to be > 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 Preclinical safety data

No animal studies are known to be conducted with Sitagliptin + Metformin.

Known animal studies on dogs treated with either metformin alone or a combination of metformin and sitagliptin are not known to show additional toxicity from the combination. The NOEL in these studies are known to be 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 known to be performed with sitagliptin or metformin individually.

Sitagliptin

Renal and liver toxicity were known in rodents at systemic exposure values 58 times the human exposure level, while the no-effect level is known to be 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 are known to be observed in dogs at exposure levels approximately 23 times the clinical exposure level. In addition, very slight to slight skeletal muscle degeneration is also known to be observed histologically at doses resulting in systemic exposure levels of approximately 23 times the human exposure level. A no-effect level for these findings is known at an exposure 6-fold the clinical exposure level.

Sitagliptin has not been demonstrated to be genotoxic in known preclinical studies. Sitagliptin is not known to be carcinogenic in mice. In rats, there may be an increased incidence of hepatic adenomas and carcinomas at systemic exposure levels 58 times the human exposure level. Since hepatotoxicity is known to correlate with induction of hepatic neoplasia in rats, this increased incidence of hepatic tumors in rats may likely be 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 may not be considered relevant for the situation in humans.

No treatment related effects on fertility are known in male and female rats given sitagliptin prior to and throughout mating.

Known data from a pre-/post-natal development study in rats sitagliptin are not known to show adverse effects.

Known reproductive toxicity studies are known to show a slight treatment-related increased incidence of fetal rib malformations (absent, hypo plastic and wavy ribs) in the offspring of rats atsystemic 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 known to be secreted in considerable amounts into the milk of lactating rats (milk/plasma ratio: 4:1).

Metformin
Preclinical data for metformin are not known to reveal special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction

6. Pharmaceutical particulars

6.1 List of excipients

In the tablet core:

- Microcrystalline cellulose (PH-102)
- Povidone K-30
- Sodium lauryl sulfate
- Colloidal anhydrous silica
- Sodium stearyl fumarate.

In addition, the film coating contains:

- Color coat FC 4W-H
- Orange red lake color 2028.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage:

Do not store above 30℃

6.5 Nature and contents of container

Blisters (Alu/alu).
Packs of 14 film-coated tablets.

6.6 Special precautions for disposal and other handling:
No special requirements.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorisation holder
Martin Dow Limited
Plot 37, Sector 19, Korangi Industrial Area, Karachi-74900, Pakistan

Manufacturing site address
Martin Dow Limited
Plot 37, Sector 19, Korangi Industrial Area, Karachi-74900, Pakistan

Local Technical Representative
Cintana Healthcare Services Ltd

8. Marketing authorization number
CTD9840

9. Date of first registration
03/03/2023

10. Date of revision of the text:
26/11/2021

11. Dosimetry:
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:
Not Applicable