SUMMARY OF PRODUCT CHARACTERISTICS

INSTADIP M-ER

(Sitagliptin + Metformin ER Tablets 50+500mg)

1. NAME OF THE MEDICINAL PRODUCT

SITAGLIPTIN + METFORMIN ER TABLETS 50+500MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

INSTADIP M-ER

Each film coated tablet contains
62.03 mg of Sitagliptin phosphate USP equivalent to Sitagliptin 50 mg
Metformin HCl Ph Eur. 500
Excipients qs
Colour: Titanium Dioxide, FD & C Blue

For the full list of excipients, see **section 6.1.**

3. PHARMACEUTICAL FORM

Extended release tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sitagliptin + Metformin ER Tablets is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin is appropriate.

4.2 Posology and method of administration

Sitagliptin + Metformin ER Tablets is available as fixed dose combination of sitagliptin and metformin in the strength of 50/500 mg, 50/1000 mg and 100/1000 mg only and may not be suitable for all the dosing recommendations mentioned below. In such cases, other suitable approved strengths/dosage forms of sitagliptin and metformin should be used.

Life-threatening lactic acidosis can occur due to accumulation of metformin. Risk

factors include renal impairment, old age and the use of high doses of metformin above 2000 mg per day.

General

The dosage of anti-hyperglycaemic therapy with Sitagliptin + Metformin ER Tablets 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 and 2000 mg metformin.

Sitagliptin + Metformin ER Tablets should be given once daily with a meal preferably in the evening. The dose should be escalated gradually to reduce the gastrointestinal (GI) side effects due to metformin. Additionally, administration of Sitagliptin + Metformin ER Tablets with food enhances plasma concentrations of metformin. To preserve the modified-release properties, the tablets must not be split, broken, crushed, or chewed before swallowing. There have been reports of incompletely dissolved sitagliptin and metformin extended release tablets being eliminated in the faeces. It is not known whether this material seen in faeces contains active drug.

If a patient reports repeatedly seeing tablets in faeces, the healthcare provider should assess adequacy of glycaemic control.

Dosage

The starting dose of Sitagliptin + Metformin ER Tablets should be based on the patient's current regimen. Sitagliptin + Metformin ER Tablets should be given once daily with a meal preferably in the evening.

Sitagliptin + Metformin ER Tablets are available in the following strengths:
50 mg sitagliptin/500 mg extended release metformin hydrochloride
50 mg sitagliptin/1000 mg extended release metformin hydrochloride
100 mg sitagliptin/1000 mg extended release metformin hydrochloride

For patients using the 50 mg sitagliptin/500 mg metformin hydrochloride extended release tablet or the 50 mg sitagliptin/1000 mg metformin hydrochloride extended release tablet, two tablets should be taken together once daily. The 100 mg sitagliptin/1000 mg metformin hydrochloride extended release tablet should be taken as a single tablet once daily.

As initial therapy

For patients with type 2 diabetes mellitus, whose hyperglycaemia is inadequately controlled with diet and exercise alone, when dual therapy is appropriate, the

recommended total daily starting dose of Sitagliptin + Metformin ER Tablets is 100 mg sitagliptin and 1000 mg metformin hydrochloride. Patients with inadequate glycaemic control on this dose should have their metformin dose increased up to a maximum of 100 mg sitagliptin/2000 mg metformin hydrochloride daily.

For patients inadequately controlled on sitagliptin monotherapy
For patients inadequately controlled on sitagliptin alone, the recommended starting dose of Sitagliptin + Metformin ER Tablets is 100 mg sitagliptin and 1000 mg metformin hydrochloride daily. Patients may be titrated up to 100 mg sitagliptin/2000 mg metformin hydrochloride daily to achieve glycaemic control. Patients taking sitagliptin monotherapy dose-adjusted for renal impairment should not be switched to Sitagliptin + Metformin ER Tablets (see **section 4.3**).

For patients inadequately controlled on metformin monotherapy
For patients not adequately controlled on metformin alone, the usual starting dose of Sitagliptin + Metformin ER Tablets should provide sitagliptin 100 mg total daily dose plus the dose of metformin already being taken.

For patients switching from sitagliptin co-administered with metformin
For patients switching from sitagliptin co-administered with metformin, Sitagliptin + Metformin ER Tablets may be initiated at the dose of sitagliptin and metformin already being taken.

For patients inadequately controlled on dual combination therapy with metformin and a sulfonylurea
The usual starting dose of Sitagliptin + Metformin ER Tablets should provide sitagliptin 100 mg total daily dose and the dose of metformin already being taken. Patients may require lower sulfonylurea doses to reduce the risk of sulfonylurea-induced hypoglycaemia (see **section 4.4**).

For patients inadequately controlled on dual combination therapy with metformin and insulin
The usual starting dose of Sitagliptin + Metformin ER Tablets should provide 100 mg total daily dose of sitagliptin. In determining the starting dose of the metformin component, the patient's level of glycaemic control and current dose of metformin should be considered. Patients currently on or initiating insulin therapy may require lower doses of insulin to reduce the risk of hypoglycaemia (see **section 4.4**).

Recommendations for use in renal impairment

No dose adjustment is needed for patients with mild renal impairment (estimated glomerular filtration rate [eGFR] ≥ 60 mL/min/1.73 m^2). An eGFR should be assessed before initiation of treatment with sitagliptin/metformin and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase risk of lactic acidosis (see **section 4.4**) should be reviewed before considering initiation of metformin in patients with eGFR < 60 mL/min/1.73 m^2. See table below for recommended daily dose.

Sitagliptin + Metformin ER Tablets is prescribed once daily.
Sitagliptin + Metformin ER Tablets is contraindicated in patients with eGFR < 30 mL/min/1.73 m^2. Discontinue Sitagliptin + Metformin ER Tablets if the patient's eGFR later falls below 30 mL/min/1.73 m^2 (see **sections 4.3** and **4.4**). Initiation of Sitagliptin + Metformin ER Tablets in patients with an eGFR ≥ 30 mL/min/1.73 m^2 and < 45 mL/min/1.73 m^2 is not recommended. In patients taking Sitagliptin + Metformin ER Tablets whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit and risk of continuing therapy and limit dose of the sitagliptin component to 50 mg once day.

eGFR mL/min/1.73 m^2	**Metformin**	**Sitagliptin**
60-89	Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.	Maximum daily dose is 100 mg.
45-59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 100 mg.
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 50 mg.
< 30	Metformin is contraindicated.	Maximum daily dose is 25 mg.

Discontinuation for iodinated contrast imaging procedures
Discontinue Sitagliptin + Metformin ER Tablets at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR ≥ 30 to < 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart Sitagliptin + Metformin ER Tablets if renal function is acceptable (see **section 4.4**).

Elderly

As metformin and sitagliptin are excreted by the kidney, Sitagliptin + Metformin ER Tablets 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 **section 4.4**).

Paediatric Population
Sitagliptin/metformin should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy. There are no reported studies on sitagliptin/metformin in children younger than 10 years of age.

Previous therapies
No studies have been reported specifically examining the safety and efficacy of sitagliptin/metformin in patients previously treated with other oral anti-hyperglycaemic agents and switched to sitagliptin/metformin. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycaemic control can occur.

4.3 Contraindications

Sitagliptin + Metformin ER Tablets (sitagliptin/metformin) is contraindicated in patients with:

- known hypersensitivity to sitagliptin, metformin or any of the excipients listed in section 6.1;
- severe renal impairment (eGFR < 30 mL/min/1.73 m^2) (see **section 4.4**);
- acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.

Sitagliptin/metformin should be temporarily discontinued in patients undergoing radiological studies involving intravascular administration of iodinated contrast materials, because the use of such products may result in acute alteration of renal function (see **section 4.4**).

Sitagliptin + Metformin ER Tablets is not currently indicated for use in children below 18 years.

4.4 Special warnings and precautions for use

Sitagliptin /metformin

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

Pancreatitis: There have been reports of acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotising pancreatitis (see **section 4.8**), in patients taking sitagliptin. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been reported after discontinuation of sitagliptin. If pancreatitis is suspected, sitagliptin/metformin and other potentially suspect medicinal products should be discontinued.

Monitoring 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. Sitagliptin/metformin is contraindicated in severe renal impairment, patients with an eGFR < 30 mL/min/1.73 m^2 (see **section 4.2**, **4.3** and **4.4**, ***Metformin***, *Lactic acidosis*).

Before initiation of therapy with sitagliptin/metformin and at least annually thereafter, renal function should be assessed. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and sitagliptin/metformin discontinued if evidence of renal impairment is present.

Sitagliptin

Hypoglycaemia
In reported clinical trials of sitagliptin as monotherapy and as part of combination therapy with agents not known to cause hypoglycaemia (i.e. metformin or pioglitazone), rates of hypoglycaemia reported with sitagliptin were similar to rates in patients taking placebo. As is typical with other anti-hyperglycaemic agents, hypoglycaemia has been reported when sitagliptin were used in combination with insulin or a sulfonylurea (see Section 4.8). Therefore, to reduce the risk of sulfonylurea- or insulin-induced hypoglycaemia, a lower dose of sulfonylurea or insulin may be considered (see **section 4.2**).

Hypersensitivity Reactions
There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of sitagliptin/metformin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue sitagliptin/metformin,

assess for other potential causes for the event, and institute alternative treatment for diabetes (see **sections 4.3** and **4.8**).

Arthralgia
There have been post-marketing reports of joint pain, which may be severe, in patients taking DPP-4 inhibitors. Onset of symptoms following initiation of treatment may be rapid or may occur after longer periods. Discontinuation of therapy should be considered in patients who present with or experience an exacerbation of joint symptoms during treatment with DPP-4 inhibitors.

Bullous Pemphigoid
Postmarketing cases of bullous pemphigoid requiring hospitalisation have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving sitagliptin/metformin. If bullous pemphigoid is suspected, sitagliptin/metformin should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Metformin

Lactic Acidosis
Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with sitagliptin/metformin; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxaemia. Lactic acidosis is characterised by elevated blood lactate levels (> 5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels > 5 microgram/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications (see **section 4.2**). Patients with congestive heart failure requiring pharmacologic management, in particular

those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxaemia, are at increased risk of lactic acidosis.

The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function (see **section 4.4**, ***Use in elderly***). In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxaemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure.

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilised on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonaemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued

immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialysable (with a clearance of up to 170 mL/min under good haemodynamic conditions), prompt haemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery (see **section 4.3**).

Hypoglycaemia
Hypoglycaemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycaemic effects. Hypoglycaemia may be difficult to recognise in the elderly, and in people who are taking β-adrenergic blocking drugs.

Use of concomitant medications that may affect renal function or metformin disposition
Concomitant medication(s) that may affect renal function or result in significant haemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see **section 4.5**), should be used with caution.

Radiological studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials)
Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been reported to be associated with lactic acidosis in patients receiving metformin (see **section 4.3**). Therefore, in patients with an eGFR ≥ 30 to < 60 mL/min/1.73 m^2, in patients with a history of hepatic impairment, alcoholism, or heart failure, or in patients who will be administered intra-arterial iodinated contrast, sitagliptin/metformin should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be acceptable (see **section 4.2**).

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

Surgical procedures
Use of sitagliptin/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 acceptable (see **section 4.2**).

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 sitagliptin/metformin.

Impaired hepatic function
Since impaired hepatic function has been reported to be associated with some cases of lactic acidosis, sitagliptin/metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} levels
In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was reported in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation. Measurement of haematologic parameters on an annual basis is advised in patients on sitagliptin/metformin and any apparent abnormalities should be appropriately investigated and managed.

Certain individuals (those with inadequate Vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B_{12} levels. In these patients, routine serum Vitamin B_{12} measurements at two- to three-year intervals may be useful.

Change in clinical status of patients with previously controlled type 2 diabete
A patient with type 2 diabetes previously well controlled on sitagliptin/metformin 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, sitagliptin/metformin must be stopped immediately and other appropriate corrective measures initiated.

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

Use in the elderly

Sitagliptin/metformin

Because sitagliptin and metformin are substantially excreted by the kidney and because aging can be associated with reduced renal function, sitagliptin/metformin should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function (See **section 4.4**).

Sitagliptin phosphate monohydrate
The safety and effectiveness of sitagliptin in the elderly (≥ 65 years,) have been reported to be comparable to younger patients (< 65 years).

Metformin hydrochloride
The reported studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Paediatric use

Safety and effectiveness of sitagliptin/metformin in paediatric patients under 18 years have not been established.

Sitagliptin/metformin should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy. Sitagliptin has been reported to be associated with an increased risk of hypoglycaemia in paediatric patients on or not on background insulin (see **section 4.8**).

There are no reported studies on sitagliptin/metformin in paediatric patients under 10 years of age.

Effects on laboratory tests

Sitagliptin

The incidence of laboratory adverse experiences has been reported to be similar in patients treated with sitagliptin and metformin (7.6%) compared to patients treated with placebo and metformin (8.7%). A small increase in white blood cell count (approximately 200 cells/microL difference in WBC vs placebo; mean baseline WBC approximately 6600 cells/microL) has been reported due to a small increase in neutrophils. This observation has been reported in most but not all studies. This change in laboratory parameters is not considered to be clinically relevant.

Metformin

In reported studies of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, has been reported in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation (see **section 4.4**).

4.5 Interaction with other medicinal products and other forms of interaction

Sitagliptin and Metformin
Co-administration of multiple doses of sitagliptin (50 mg b.i.d.) and metformin (1000 mg b.i.d.) did not meaningfully alter the pharmacokinetics of either sitagliptin or metformin in patients with type 2 diabetes.

Pharmacokinetic drug interaction studies with sitagliptin/metformin have not been reported; however, such studies have been reported with the individual components of sitagliptin/metformin.

Sitagliptin

***In Vitro* Assessment of Drug Interactions**
Sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6 at therapeutic concentrations, and is not an inducer of CYP3A4. Sitagliptin is a p-glycoprotein substrate, but does not inhibit p-glycoprotein mediated transport of digoxin. Based on these results, sitagliptin is considered unlikely to cause interactions with other drugs that utilise these pathways.

Sitagliptin is not extensively bound to plasma proteins. Therefore, the propensity of sitagliptin to be involved in clinically meaningful drug-drug interactions mediated by plasma protein binding displacement is very low.

***In Vivo* Assessment of Drug Interactions**

Effect of Sitagliptin on Other Drugs

In reported clinical studies, as described below, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glibenclamide, ertugliflozin, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT). Multiple doses of sitagliptin have been reported to slightly increase digoxin concentrations; however, these increases are not considered likely to be clinically meaningful and are not attributed to a specific mechanism.

Sulfonylureas: Single-dose pharmacokinetics of glibenclamide, a CYP2C9 substrate, have not been reported to be meaningfully altered in subjects receiving multiple doses of sitagliptin. Clinically meaningful interactions would not be expected with other sulfonylureas (e.g. glipizide, tolbutamide, and glimepiride) which, like glibenclamide, are primarily eliminated by CYP2C9.

Ertugliflozin: Single-dose administration of sitagliptin 100 mg had no clinically meaningful effect on the exposure of ertugliflozin 15 mg. The geometric mean ratios (GMR) and 90% CI (expressed as percentages) for ertugliflozin AUC_{inf} and C_{max} for co-administration with sitagliptin vs. ertugliflozin alone have been reported to be 102.27% (99.72%, 104.89%) and 98.18% (91.20%, 105.70%), respectively.

Simvastatin: Single-dose pharmacokinetics of simvastatin, a CYP3A4 substrate, have not been reported to be meaningfully altered in subjects receiving multiple daily doses of sitagliptin. Therefore, sitagliptin is not an inhibitor of CYP3A4-mediated metabolism.

Thiazolidinediones: Single-dose pharmacokinetics of rosiglitazone have not been reported to be meaningfully altered in subjects receiving multiple daily doses of sitagliptin. Therefore, sitagliptin is not an inhibitor of CYP2C8-mediated metabolism. Clinically meaningful interactions with pioglitazone are not expected because pioglitazone predominantly undergoes CYP2C8- or CYP3A4-mediated metabolism.

Warfarin: Multiple daily doses of sitagliptin did not meaningfully alter the pharmacokinetics, as assessed by measurement of S(-) or R(+) warfarin enantiomers, or pharmacodynamics (as assessed by measurement of prothrombin INR) of a single dose of warfarin. Since S(-) warfarin is primarily metabolised by CYP2C9, these data also support the conclusion that sitagliptin is not a CYP2C9 inhibitor.

Oral Contraceptives: Co-administration with sitagliptin did not meaningfully alter the

steady-state pharmacokinetics of norethindrone or ethinyl estradiol.

Digoxin: Sitagliptin had a minimal effect on the pharmacokinetics of digoxin. Following administration of 0.25 mg digoxin concomitantly with 100 mg of sitagliptin daily for 10 days, the plasma AUC of digoxin has been reported to increase by 11%, and the plasma C_{max} by 18%. These increases are not considered to be clinically meaningful.

Effect of Other Drugs on Sitagliptin
The reported clinical data described below suggest that sitagliptin is not susceptible to clinically meaningful interactions by co-administered medications:

Ertugliflozin: No clinically meaningful change in sitagliptin exposure has been reported following concomitant administration of a single 100 mg sitagliptin dose with 15 mg ertugliflozin compared to sitagliptin alone. The GMR and 90% CI (expressed as percentages) for sitagliptin AUC_{inf} and C_{max} for co-administration with ertugliflozin vs. sitagliptin alone have been reported to be 101.67% (98.40%, 105.04%) and 101.68% (91.65%, 112.80%), respectively.

Ciclosporin: Co-administration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of ciclosporin reportedly increased the AUC and C_{max} of sitagliptin by approximately 29% and 68%, respectively. These modest changes in sitagliptin pharmacokinetics have not been reported to be clinically meaningful. The renal clearance of sitagliptin has also not been reported to be meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

Population Pharmacokinetics: Population pharmacokinetic analyses have been reported in patients with type 2 diabetes. Concomitant medications did not reportedly have a clinically meaningful effect on sitagliptin pharmacokinetics. Medications reportedly assessed were those that are commonly administered to patients with type 2 diabetes including cholesterol-lowering agents (e.g. statins, fibrates, ezetimibe), anti-platelet agents (e.g. clopidogrel), antihypertensives (e.g. ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, hydrochlorothiazide), analgesics and non-steroidal anti-inflammatory agents (e.g. naproxen, diclofenac, celecoxib), anti-depressants (e.g. bupropion, fluoxetine, sertraline), antihistamines (e.g. cetirizine), proton-pump inhibitors (e.g. omeprazole, lansoprazole), and medications for erectile dysfunction (e.g. sildenafil).

Metformin
Glibenclamide: In a reported study in type 2 diabetes patients, co-administration of metformin and glibenclamide did not result in any changes in either metformin

pharmacokinetics or pharmacodynamics. Decreases in glibenclamide AUC and C_{max} were reported, but were highly variable. The single-dose nature of this study and the lack of correlation between glibenclamide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

Furosemide (Frusemide): Pharmacokinetic parameters of both metformin and furosemide have been reported to be affected by co-administration. Frusemide reportedly increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of frusemide have been reported to be 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life has been reported to decrease by 32%, without any significant change in frusemide renal clearance. No information is available about the interaction of metformin and frusemide when co-administered chronically.

Nifedipine: Co-administration of nifedipine reportedly increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Drugs that reduce metformin clearance: 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.

Other: Certain drugs tend to produce hyperglycaemia and may lead to loss of glycaemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, oestrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving sitagliptin/metformin the patient should be closely observed to maintain adequate glycaemic control.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen have not been reported to be affected when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and

probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

4.6 Fertility, Pregnancy and lactation

Fertility

There are no reported studies with the combined components of sitagliptin/metformin to evaluate the effects on fertility.

Sitagliptin

No adverse effects on fertility have been reported in male and female rats given sitagliptin orally at doses up to 1000 mg/kg daily (up to approximately 100 times the human exposure based on the recommended daily adult human dose of 100 mg/day) prior to and throughout mating.

Metformin hydrochloride

Fertility of male or female rats has been reported to be unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

Pregnancy (Category C)

No adequate and well-controlled studies have been reported in pregnant women with sitagliptin/metformin or its individual components; therefore, the safety of sitagliptin/metformin in pregnant women is not known. Sitagliptin/metformin, like other oral antihyperglycaemic agents, are not recommended for use in pregnancy.

No animal studies have been reported with the combined components of sitagliptin/metformin to evaluate effects on reproduction. The following data are based on findings in studies reported with sitagliptin or metformin individually.

Sitagliptin

Sitagliptin has not been reported to be teratogenic in rats at oral doses up to 250 mg/kg/day or in rabbits given up to 125 mg/kg/day during organogenesis (up to 32 and 22 times, respectively, the human exposure based on the recommended daily adult human dose of 100 mg). In rats, a slight increase in the incidence of fetal rib malformations (absent, hypoplastic and wavy ribs) has been reported at oral doses of 1000 mg/kg/day (approximately 100 times the human exposure based on the recommended daily adult human dose of 100 mg). Slight decreases in mean birth weight and preweaning and postweaning body weight gains have been reported in the offspring of rats given sitagliptin at an oral dose of 1000 mg/kg/day from gestation day 6 to lactation day 20.

However, animal reproduction studies are not always predictive of the human response. Sitagliptin crosses the placenta in rats and rabbits.

Metformin
Metformin has not been reported to be teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This dose is about 3 and 6 times the maximum recommended human daily dose of 2,000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of foetal concentrations reported a partial placental barrier to metformin.

Lactation
No studies in lactating animals have been reported with the combined components of sitagliptin/metformin. In studies reported with the individual components, both sitagliptin and metformin were excreted in the milk of lactating rats. For sitagliptin, excretion has been reported at a milk to plasma ratio of 4:1. Treatment of rats with sitagliptin during pregnancy and lactation reportedly caused decreased pup body weight gain. It is not known whether sitagliptin is excreted in human milk; some excretion of metformin in human milk has been reported. Therefore, sitagliptin/metformin should not be used by a woman who is nursing.

4.7 Effects on ability to drive and use machines

No studies of the effects of sitagliptin/metformin on the ability to drive and use machines have been reported. However, sitagliptin/metformin is not expected to affect the ability to drive and use machines.

4.8 Undesirable effects

Reported clinical studies
In reported studies, in patients with type 2 diabetes mellitus on metformin monotherapy, the addition of sitagliptin 100 mg daily was well tolerated. The overall incidence of adverse experiences reported in patients receiving sitagliptin and metformin was similar to that reported with patients receiving placebo and metformin.

In another reported study of initial therapy with sitagliptin in combination with metformin, the adverse reactions reported (regardless of investigator assessment of causality) in ≥ 5% of patients are shown in table below.

Table: Initial Therapy with Combination of Sitagliptin and Metformin: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥ 5% of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Placebo)†

	Placebo/ Metformin 1000 mg bid (%)	Sitagliptin 100 mg QD (%)	Metformin 500 or 1000 mg bid†† (%)	Sitagliptin 50 mg bid + Metformin 500 or 1000 mg bid†† (%)
Diarrhoea	6.8	4.5	10.1	11.8
Nausea	2.3	1.1	6.9	5.9
Bronchitis	4.5	1.7	3.8	7.3
Influenza	2.8	4.5	6.9	5.4
Upper Respiratory Tract Infection	7.4	6.7	10.2	12.1
Urinary Tract Infection	2.3	0	5.8	5.1
Arthralgia	1.7	3.9	4.9	5.4
Back Pain	5.1	5.0	4.4	6.5
Headache	4.0	3.4	5.8	7.3

† Intent-to-treat population.
†† Data pooled for the patients given the lower and higher doses of metformin.

The reported adverse reactions of hypoglycaemia were based on all reports of hypoglycaemia; a concurrent glucose measurement was not required. The overall incidence of pre-specified adverse reactions of hypoglycaemia in patients with type 2 diabetes mellitus inadequately controlled on diet and exercise has been reported to be 2.8% in patients given placebo, 1.1% in patients given sitagliptin alone, 1.9% in patients given metformin alone and 3.8% in patients given sitagliptin in combination with metformin.

With the combination of sitagliptin and metformin, no clinically meaningful changes in vital signs or in ECG (including in QTc interval) have been reported.

Treatment-emergent adverse events have been reported in similar numbers across all treatment groups. Over the two-year treatment period, discontinuation due to loss of efficacy was has been reported more commonly in the 100 mg sitagliptin group than other treatment groups.

Adverse reactions reported in 2% to 5% of patients treated with sitagliptin and metformin in this reported study and at least 2 fold more commonly than in patients treated with metformin are listed below:

Infections and Infestations: Bronchitis, Sinusitis
Nervous System Disorders: Headache

Musculoskeletal and Connective Tissue Disorders: Arthralgia
Respiratory, Thoracic and Mediastinal Disorders: Pharyngolaryngeal Pain

Sitagliptin as add-on Combination Therapy to Metformin
No adverse experiences have been reported with sitagliptin 100 mg administered once daily added to a twice daily metformin regimen (> 1500 mg) regardless of investigator assessment of causality in ≥ 5% of patients and more commonly than in patients given placebo. Discontinuation of therapy due to clinical adverse experiences has been reported to be similar to the placebo treatment group (sitagliptin and metformin, 1.9%; placebo and metformin, 2.5%).

Hypoglycaemia and Gastrointestinal Adverse Experiences
The incidence of hypoglycaemia (regardless of investigator assessment of causality) in patients treated with the combination of sitagliptin and metformin has been reported to be similar to patients treated with metformin and placebo. Adverse experiences of hypoglycaemia were based on all reports of hypoglycaemia; a concurrent glucose measurement was not required. The incidences of pre-specified gastrointestinal adverse experiences in patients treated with the combination of sitagliptin and metformin were similar to those reported for patients treated with metformin alone (see table below).

Table: Hypoglycaemia and Pre-specified Gastrointestinal Intestinal Adverse Experiences (Regardless of Investigator Assessment of Causality) Reported in Patients Receiving Combination Therapy

	Number of patients (%)	
	Reported study of sitagliptin as add-on to metformin	
	Placebo and Metformin ≥ 1500 mg daily (%)	**Sitagliptin 100 mg and Metformin ≥ 1500 mg daily (%)**
Hypoglycaemia	2.1	1.3
Diarrhoea	2.5	2.4
Nausea	0.8	1.3
Vomiting	0.8	1.1
Abdominal Pain	3.8	2.2

With the combination of sitagliptin and metformin, no clinically meaningful changes in vital signs or in ECG (including in QTc interval) have been reported.

Adverse reactions reported in 2% to 5% of patients treated with sitagliptin and metformin and at least 2 fold more commonly than in patients treated with metformin and placebo are listed below:

Musculoskeletal and Connective Tissue Disorders: Arthralgia

Sitagliptin as Add-on Combination Therapy with Metformin and a Sulfonylurea

In a reported study of sitagliptin as add-on combination therapy with metformin and a sulfonylurea (placebo-controlled for 24 weeks, followed by a 30-week active-controlled phase), the only adverse experience reported regardless of investigator assessment of causality in ≥ 5% of patients and more commonly than in patients given placebo was hypoglycaemia (see table below). Discontinuation of therapy due to clinical adverse experiences has been reported to be similar to the control group (at 24 weeks, sitagliptin, metformin, and sulfonylurea, 1.0% vs placebo, metformin, and sulfonylurea 1.4%; at 54 weeks, sitagliptin, metformin, and sulfonylurea, 1.4% vs placebo/pioglitazone, metformin, and sulfonylurea 3.8%).

Table: Hypoglycaemia (Regardless of Investigator Assessment of Causality) Reported in Patients Receiving Combination Therapy

	Number of patients (%)	
	Reported Study of Sitagliptin as Add-on to Metformin and Sulfonylurea	
	Sitagliptin + Metformin + Sulfonylurea	**Placebo + Metformin + Sulfonylurea**
Metabolism and Nutrition Disorders		
Hypoglycaemia	14.8%‡	4.7%‡

‡ Weeks 0-24

Hypoglycaemia has been reported in 18.1% patients treated with sitagliptin + metformin + sulfonylurea compared to 14.6% patients in the control group (placebo + metformin + sulfonylurea for 24 weeks followed by pioglitazone + metformin + sulfonylurea for 30 weeks). Symptomatic episodes assessed as likely to be hypoglycaemia have been reported as adverse experiences regardless of whether fingerstick blood glucose determination was performed at the time of symptoms. Severe hypoglycaemia has been reported in 1.0% patients treated with sitagliptin + metformin + sulfonylurea compared to one patient 0.5% treated with placebo/pioglitazone + metformin + sulfonylurea.

Adverse reactions reported in 2% to 5% of patients treated with sitagliptin, metformin and a sulfonylurea in this reported study and at least 2 fold more commonly than in patients treated with placebo, metformin and a sulfonylurea are listed below:

Infections and Infestations: Influenza, Nasopharyngitis
Musculoskeletal and Connective Tissue Disorders: Pain in Extremity

Sitagliptin in Combination with Metformin and Insulin

In a reported study of sitagliptin 100 mg once daily added to ongoing combination treatment with metformin and stable-dose insulin, the only adverse experience reported

regardless of causality assessment in ≥ 5% of patients treated with sitagliptin and more commonly than in patients treated with placebo was hypoglycaemia (see table below); the incidence of discontinuation due to clinical adverse reactions has been reported to be slightly higher than placebo (discontinuation rates: add-on to insulin, with or without metformin, 3.4% vs placebo and insulin, with or without metformin, 1.3%).

Table: Hypoglycaemia (Regardless of Investigator Assessment of Causality) Reported in Patients Receiving Combination Therapy

	Number of patients (%)	
	Study of Sitagliptin as Add-on to Insulin and Metformin	
	Sitagliptin 100 mg + Insulin + Metformin	**Placebo + Insulin + Metformin**
Metabolism and Nutrition Disorders		
Hypoglycaemia	15.3%	8.2%

Adverse reactions reported in 2% to 5% of patients treated with sitagliptin, metformin and insulin in this reported study and at least 2 fold more commonly than in patients treated with placebo, metformin and insulin are listed below:

Nervous system disorders: Headache

Sitagliptin in Combination with Metformin and Ertugliflozin

The safety of sitagliptin used in combination with metformin and the SGLT2 inhibitor ertugliflozin has been reported in patients with type 2 diabetes mellitus treated for 26 weeks. The incidence and type of adverse reactions have been reported to be consistent with that reported with the individual components, sitagliptin, metformin and ertugliflozin.

Pancreatitis

The incidence of non-adjudicated acute pancreatitis events has been reported to be 0.1 per 100 patient-years in patients treated with sitagliptin 100 mg/day or corresponding (active or placebo) control (see **section 4.4**).

In another reported 24-week study of patients receiving sitagliptin as add-on therapy while undergoing insulin intensification (with or without metformin), the only drug-related adverse reaction reported in ≥ 1% in patients treated with sitagliptin and metformin and more commonly than in patients treated with placebo and metformin was vomiting (sitagliptin and metformin, 1.1%; placebo and metformin, 0.4%).

Adverse Reactions Reported with Sitagliptin

The most common adverse experience in sitagliptin monotherapy reported regardless of investigator assessment of causality in ≥ 5% of patients and more commonly than in patients given placebo was nasopharyngitis.

Adverse Reactions Reported with Metformin

The most commonly (> 5%) reported adverse experiences due to initiation of metformin therapy are diarrhoea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

Reported TECOS Cardiovascular Safety Study

The reported Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 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 patients treated with placebo in the intention-to treat population. Both treatments were reportedly added to usual care targeting regional standards for HbA1c and CV risk factors. The overall incidence of serious adverse events in patients receiving sitagliptin has been reported to be 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 hypoglycaemia has been reported to be 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 hypoglycaemia has been reported to be 1.0% in sitagliptin-treated patients and 0.7% in placebo-treated patients. The incidence of adjudication-confirmed pancreatitis events has been reported to be 0.3% in sitagliptin-treated patients and 0.2% in placebo-treated patients.

Paediatric population

The profile of adverse reactions with sitagliptin/metformin in patients aged 10 to 17 years with type 2 diabetes mellitus has been reported to be comparable to that in adults. In paediatric patients on or not on background insulin, sitagliptin has been reported to be associated with an increased risk of hypoglycaemia.

Reported Post-marketing Experience

Additional adverse reactions have been reported during post-marketing use of sitagliptin/metformin or sitagliptin. These reactions have been reported when sitagliptin/metformin or sitagliptin have been used alone and/or in combination with other antihyperglycaemic agents. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and infestations: upper respiratory tract infection; nasopharyngitis
Nervous system disorders: headache
Gastrointestinal disorders: acute pancreatitis, including fatal and non-fatal haemorrhagic and necrotising pancreatitis (see **section 4.4**); constipation; vomiting
Musculoskeletal and connective tissue disorders: arthralgia; myalgia; pain in extremity; back pain
Renal and urinary disorders: worsening renal function, including acute renal failure (sometimes requiring dialysis)

Hypersensitivity reactions (including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, pruritus, bullous pemphigoid and exfoliative skin conditions, including Stevens-Johnson syndrome) have been reported with use of sitagliptin (see **section 4.3**).

4.9 Overdose

Sitagliptin
Single doses of up to 800 mg sitagliptin have been reported to be generally well tolerated in healthy subjects. Minimal increases in QTc, not considered to be clinically relevant, have been reported at a dose of 800 mg sitagliptin (see **section 5.1**). There is no experience with doses above 800 mg in humans. No dose related clinical adverse reactions have been reported with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

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

Sitagliptin is modestly dialysable. Approximately 13.5% of the dose has been reported to be 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.

Metformin
Overdose of metformin hydrochloride has been reported, including ingestion of amounts greater than 50 grams. Hypoglycaemia has been reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see **section 4.4**). Metformin is dialysable with a clearance of up to 170 mL/min under good haemodynamic conditions. Therefore, haemodialysis may be useful for removal of

accumulated drug from patients in whom metformin overdosage is suspected.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group
Drugs used in diabetes, Combinations of oral blood glucose lowering drugs; ATC code: A10BD07

Sitagliptin + Metformin ER Tablets combines two anti-hyperglycaemic agents with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: sitagliptin phosphate monohydrate, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Mechanism of action

Sitagliptin

Sitagliptin is a member of a class of oral anti-hyperglycaemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors, which improve glycaemic control in patients with type 2 diabetes by enhancing the levels of active incretin hormones.

Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signalling pathways involving cyclic AMP. Treatment with GLP-1 or with DPP-4 inhibitors in animal models of type 2 diabetes has been reported to improve beta cell responsiveness to glucose and stimulate insulin biosynthesis and release. With higher insulin levels, tissue glucose uptake is enhanced. In addition, GLP-1 lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon concentrations, along with higher insulin levels, lead to reduced hepatic glucose production, resulting in a decrease in blood glucose levels. The effects of GLP-1 and GIP are glucose dependent such that when blood glucose concentrations are low, stimulation of insulin release and suppression of glucagon secretion by GLP-1 are not observed. For both GLP-1 and GIP, stimulation of insulin release is enhanced as glucose rises above normal concentrations. Further, GLP-1 does not impair the normal

glucagon response to hypoglycaemia. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyses the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in a glucose-dependent manner. This glucose-dependent mechanism is unlike the mechanism reported with sulfonylureas, whereby insulin is released even when glucose levels are low and can lead to hypoglycaemia in patients with type 2 diabetes and in normal subjects. In patients with type 2 diabetes with hyperglycaemia, these changes in insulin and glucagon levels lead to lower haemoglobin A1c (HbA1c) and lower fasting and postprandial glucose concentrations. Sitagliptin inhibits DPP-4 with nanomolar potency (IC_{50} 18 nM). It does not inhibit the closelyrelated enzymes DPP-8 or DPP-9 at therapeutic concentrations. Inhibition of DPP-8 or DPP9 is reported to be associated with toxicity in preclinical animal models and alteration of immune function *in vitro*.

In patients with type 2 diabetes, administration of single oral doses of sitagliptin leads to inhibition of DPP-4 enzyme activity for a 24-hour period, resulting in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, increased plasma levels of insulin and C-peptide, decreased glucagon concentrations, reduced fasting glucose, and reduced glucose excursion following an oral glucose load or a meal.

In reported Phase III clinical studies of 18- and 24-week duration, treatment with sitagliptin 100 mg daily in patients with type 2 diabetes significantly improved beta cell function, as assessed by several markers, including HOMA-β (Homeostasis Model Assessment-β), proinsulin to insulin ratio, and measures of beta cell responsiveness from the frequently-sampled meal tolerance test. In reported Phase II studies, sitagliptin 50 mg twice daily provided similar glycaemic efficacy compared to sitagliptin 100 mg once daily.

In a reported study in healthy adult subjects, the effects on post-meal plasma concentrations of active and total GLP-1 and glucose after co-administration of sitagliptin and metformin were compared with those after administration of sitagliptin alone, metformin alone or placebo, each administered for two days. The incremental 4-hour post-meal weighted mean active GLP-1 concentrations were increased approximately 2-fold after either administration of sitagliptin alone or metformin alone compared with placebo. The effect on active GLP-1 concentrations after co-administration of sitagliptin and metformin were additive, with active GLP-1 concentrations increased by approximately 4-fold compared with placebo. Sitagliptin alone increased only active GLP-1 concentrations, reflecting inhibition of DPP-4, whereas metformin alone increased active and total GLP-1 concentrations to a similar extent. These reported data are

consistent with different mechanisms for the increase in active GLP-1 concentrations. Results from the reported study also demonstrated that sitagliptin, but not metformin, enhances active GIP concentrations.

Sitagliptin did not reportedly lower blood glucose or cause hypoglycaemia in healthy subjects, suggesting that the insulinotropic and glucagon suppressive actions of the drug are glucose dependent.

Effects on blood pressure
In a reported study in hypertensive patients on one or more anti-hypertensive drugs (including angiotensin-converting enzyme inhibitors, angiotensin-II antagonists, calcium-channel blockers, beta-blockers and diuretics), co-administration with sitagliptin was generally well tolerated. In these patients, sitagliptin had a modest blood pressure lowering effect; 100 mg per day of sitagliptin reduced 24-hour mean ambulatory systolic blood pressure by approximately 2 mm Hg, as compared to placebo. Reductions have not been reported in subjects with normal blood pressure.

Cardiac Electrophysiology
In a reported study, healthy subjects were administered a single oral dose of sitagliptin 100 mg, sitagliptin 800 mg (8 times the recommended dose), and placebo. At the recommended dose of 100 mg, there was no effect on the QTc interval reported at the peak plasma concentration, or at any other time during the study. Following the 800 mg dose, the maximum increase in the placebo-corrected mean change in QTc from baseline at 3 hours post-dose was 8.0 msec. This small increase has not been reported to be clinically significant. At the 800 mg dose, peak sitagliptin plasma concentrations have been reported to be approximately 11 times higher than the peak concentrations following a 100 mg dose. In patients with type 2 diabetes administered sitagliptin 100 mg or sitagliptin 200 mg daily, there were no meaningful changes in QTc interval based on ECG data reported at the time of expected peak plasma concentration.

Metformin

Metformin is an anti-hyperglycaemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral anti-hyperglycaemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilisation. Unlike sulfonylureas, metformin does not produce hypoglycaemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see **section 4.4**) and does not cause hyperinsulinaemia. With

metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

5.2 Pharmacokinetic properties

Absorption

Sitagliptin/metformin extended release

After administration of sitagliptin/metformin extended release tablets with a high-fat breakfast, the AUC for sitagliptin has not been reported to be altered. The mean C_{max} has been reported to be decreased by 17%, although the median T_{max} was unchanged relative to the fasted state. After administration of sitagliptin/metformin extended release with a high-fat breakfast, the AUC for metformin was reported to be increased 62%, the C_{max} for metformin decreased by 9%, and the median T_{max} for metformin reported to occur 2 hours later relative to the fasted state.

Sitagliptin

The absolute bioavailability of sitagliptin is reported to be approximately 87%. Co-administration of a high-fat meal reportedly had no effect on the pharmacokinetics of sitagliptin.

Metformin

The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is reported to be approximately 50-60%. The reported studies using single oral doses of metformin hydrochloride tablets 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

Food decreases the extent of and slightly delays the absorption of metformin, as reported by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Sitagliptin

The mean volume of distribution at steady state following a single 100 mg intravenous dose of sitagliptin to healthy subjects is reported to be approximately 198 litres. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).

Metformin
The reported apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride tablets, steady state plasma concentrations of metformin are reported to be reached within 24-48 hours and are generally < 1 microgram/mL. During reported studies of metformin, maximum metformin plasma levels did not exceed 5 microgram/mL, even at maximum doses.

Biotransformation

Sitagliptin
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 has been reported to be excreted as metabolites of sitagliptin. Six metabolites have been reported at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. The primary enzyme responsible for the limited metabolism of sitagliptin has been reported to be CYP3A4, with contribution from CYP2C8.

Metformin
The reported intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

Elimination

Sitagliptin
Following administration of an oral [^{14}C]sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity has been reported to be eliminated in faeces (13%) or urine (87%) within one week of dosing. The apparent terminal $t_{1/2}$ following a 100 mg oral dose of sitagliptin has been reported to be approximately 12.4 hours and renal clearance was approximately 350 mL/min.

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3),

which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporin, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

Metformin
Renal clearance is reported to be approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is reported to be eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is reported to be approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special populations

Characteristics in Patients

Type 2 Diabetes
Sitagliptin: The reported pharmacokinetics of sitagliptin in patients with type 2 diabetes are generally similar to those in healthy subjects.

Metformin: In the presence of normal renal function, there are no differences between single- or multiple-dose pharmacokinetics of metformin between patients with type 2 diabetes and normal subjects, nor is there any accumulation of metformin in either group at usual clinical doses.

Renal Impairment

Sitagliptin
An approximately 2-fold increase in the plasma AUC of sitagliptin has been reported in patients with moderate renal impairment with eGFR of 30 to < 45 mL/min/1.73 m^2, and an approximately 4-fold increase was reported in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) including patients with end-stage renal disease (ESRD) on haemodialysis, as compared to subjects with normal renal function.

Metformin
In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased (see **sections 4.3** and **4.4**).

Hepatic Impairment

Sitagliptin
In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and C_{max} of sitagliptin has been reported to increase approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100 mg dose of sitagliptin. These differences are not considered to be clinically meaningful.

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.

Metformin
No pharmacokinetic studies of metformin have been reported in patients with hepatic impairment.

Gender

Sitagliptin
Gender had no reported clinically meaningful effect on the pharmacokinetics of sitagliptin.

Metformin
Metformin pharmacokinetic parameters have not been reported to differ significantly between normal subjects and patients with type 2 diabetes when analysed according to gender. Similarly, in reported studies in patients with type 2 diabetes, the anti-hyperglycaemic effect of metformin was comparable in males and females.

Elderly

Sitagliptin
Age reportedly did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin. Elderly subjects (65 to 80 years) reportedly had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

Metformin
Limited data from reported studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is

increased, compared to healthy young subjects. From these reported data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Paediatric
The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) has been reported in paediatric patients (10 to 17 years of age) with type 2 diabetes. In this population, the dose-adjusted AUC of sitagliptin in plasma has been reported to be approximately 18% lower compared to historical data from adult patients with type 2 diabetes for a 100 mg dose.

No studies with sitagliptin have been reported in paediatric patients.

Race
Sitagliptin
Race reportedly had no clinically meaningful effect on the pharmacokinetics of sitagliptin.

Metformin
No studies of metformin pharmacokinetic parameters according to race have been reported. In reported studies of metformin in patients with type 2 diabetes, the anti-hyperglycaemic effect was comparable in whites, blacks, and Hispanics.

Body Mass Index (BMI)
Sitagliptin: Body mass index (BMI) reportedly had no clinically meaningful effect on the pharmacokinetics of sitagliptin.

5.3 Preclinical safety data

Genotoxicity
No genotoxicity studies have been reported with the combined components of sitagliptin/metformin.

Sitagliptin
Sitagliptin has not been reported to be mutagenic or clastogenic in a battery of genetic toxicology studies, including the Ames bacterial mutagenicity assay, a chromosome aberration assay in Chinese hamster ovary cells, an *in vitro* rat hepatocyte DNA alkaline elution assay (an assay which measures the compound's ability to induce single strand breaks in DNA), and an *in vivo* mouse micronucleus assay.

Metformin
There was no reported evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Reported results in the *in vivo* mouse micronucleus test were also negative.

Carcinogenicity
No carcinogenicity studies have been reported with the combined components of sitagliptin/metformin.

Sitagliptin
A reported two-year carcinogenicity study was conducted in rats given oral doses of sitagliptin of 50, 150, and 500 mg/kg/day. Increased incidence of preneoplastic lesions (altered hepatic foci) have been reported in both sexes at 150 and at 500 mg/kg/day, and hepatic adenomas and carcinomas in males and hepatic carcinomas in females at 500 mg/kg/day.

Systemic exposure in rats at 500 mg/kg/day is reported to be approximately 58 times that of humans at the recommended daily adult dose of 100 mg. This dose level has been reported to be associated with hepatotoxicity in rats. The no-observed effect level for induction of hepatic neoplasia has been reported to be 150 mg/kg/day, approximately 19-fold the human exposure at the 100 mg recommended dose. Since hepatotoxicity has been reported 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. The clinical significance of these reported findings for humans is unknown.

Sitagliptin did not reportedly increase tumour incidence at oral doses up to 500 mg/kg/day in mice (approximately 68 times human exposure at the clinical dose of 100 mg/day).

Metformin
Long-term carcinogenicity studies have been reported in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin has been reported in either male or female mice. Similarly, there was no tumourigenic potential reported with metformin in male rats. However, an increased incidence of benign stromal uterine polyps has been reported in female rats treated with 900 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose, povidone K 30, silicon dioxide, magnesium stearate, Opadry White 03F58750, Opadry Blue 20A505006, methylene chloride.

6.2 Incompatibilities

NA

6.3 Shelf life

24 Months

6.4 Special precautions for storage

NA

6.5 Nature and contents of container

10's Cold Form Blister

6.6 Special precautions for disposal and other handling

NA

7. MARKETING AUTHORISATION HOLDER

M/s Sun Pharmaceutical Industries Limited,
Village Ganguwala, Paonta Sahib- 173025
District Sirmour, Himachal Pradesh, India.

8. MARKETING AUTHORISATION NUMBER

NA

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

NA

10. DATE OF REVISION OF THE TEXT

June 2022

REFERENCES