STEMOGLIP
(Sitagliptin and Metformin Hydrochloride Film-Coated Tablets
50 mg/500 mg, 50 mg/850 mg, 50 mg/1000 mg)

1. Name of the medicinal product

STEMOGLIP
Sitagliptin and Metformin Hydrochloride Film-Coated Tablets 50 mg/500 mg
Sitagliptin and Metformin Hydrochloride Film-Coated Tablets 50 mg/850 mg
Sitagliptin and Metformin Hydrochloride Film-Coated Tablets 50 mg/1000 mg

2. Qualitative and quantitative composition

STEMOGLIP 500	STEMOGLIP 850	STEMOGLIP 1000
Each film coated tablet contains: Sitagliptin Phosphate USP Equivalent to Sitagliptin ... 50 mg Metformin Hydrochloride USP.... 500 mg	Each film coated tablet contains: Sitagliptin Phosphate USP Equivalent to Sitagliptin.... 50 mg Metformin Hydrochloride USP.... 850 mg	Each film coated tablet contains: Sitagliptin Phosphate USP Equivalent to Sitagliptin ..... 50 mg Metformin Hydrochloride USP.... 1000 mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablets
STEMOGLIP 50/500 mg Tablet: White to off white, oval shaped, film-coated tablets, debossed with 'LS' on one side and '254' on other side.

STEMOGLIP 50/850 mg Tablet: White to off white, oval shaped, film coated tablets, debossed with 'AA' on one side and plain on other side.

STEMOGLIP 50/1000 mg Tablet: White to off white, oval shaped, film coated tablets, debossed with 'LS' on one side and '255' on other side.

4. Clinical particulars

4.1 Therapeutic Indications

Sitagliptin and Metformin Hydrochloride Tablets is indicated as initial therapy in patients with type 2 diabetes mellitus to improve glycemic control when diet and exercise do not provide adequate glycemic control.

Sitagliptin and Metformin Hydrochloride Tablets is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus inadequately controlled on metformin or Sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.

Sitagliptin and Metformin Hydrochloride Tablets is indicated as part of triple combination therapy with a sulfonylurea as an adjunct to diet and exercise in patients with type 2 diabetes mellitus inadequately controlled with any two of the three agents: metformin, sitagliptin, or a sulfonylurea.

Sitagliptin and Metformin Hydrochloride Tablets is indicated as triple combination therapy with a PPARγ agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist.

Sitagliptin and Metformin Hydrochloride Tablets 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 dosage of insulin and metformin alone do not provide adequate glycemic control.

Method of administration
For oral use.

Therapeutic Class
Sitagliptin and Metformin Hydrochloride Tablets
Sitagliptin and Metformin Hydrochloride Tablets combines two antihyperglycemic agents 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 phosphate
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. This mechanism is unlike the mechanism seen with sulfonylureas; sulfonylureas cause insulin release even when glucose levels are low, which can lead to sulfonylurea-induced hypoglycemia in patients with type 2 diabetes and in normal subjects. Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations. Sitagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulfonylureas or meglitinides, biguanides, peroxisome proliferator-activated receptor gamma (PPARγ) agonists, alphaglucosidase inhibitors, and amylin analogues.

Metformin hydrochloride
Metformin is an antihyperglycemic 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 antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see PRECAUTIONS, Metformin hydrochloride) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

4.2 Posology and method of administration

General

The dosage of antihyperglycaemic therapy with Sitagliptin and Metformin Hydrochloride Tablets should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100mg sitagliptin. Initial combination therapy or maintenance of combination therapy should be individualized and left to the discretion of the health care provider.

Sitagliptin and Metformin Hydrochloride Tablets should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects associated with metformin.

The starting dose of Sitagliptin and Metformin Hydrochloride Tablets should be based on the patient's current regimen. Sitagliptin and Metformin Hydrochloride Tablets should be given twice daily with meals.

Patients inadequately controlled with diet and exercise alone:
If therapy with a combination tablet containing sitagliptin and metformin is considered appropriate for a patient with type 2 diabetes mellitus inadequately controlled with diet and exercise alone, the recommended starting dose is 50mg sitagliptin/500mg metformin hydrochloride twice daily. Patients with inadequate glycaemic control on this dose can be titrated up to 50mg sitagliptin/ 1000mg metformin hydrochloride twice daily.

Patients inadequately controlled on metformin monotherapy:
If therapy with a combination tablet containing sitagliptin and metformin is considered appropriate for a patient inadequately controlled on metformin alone, the recommended starting dose of Sitagliptin and Metformin Hydrochloride Tablets should provide sitagliptin dosed as 50mg twice daily (100mg total daily dose), and the dose of metformin already being taken.

Patients inadequately controlled on sitagliptin monotherapy:
If therapy with a combination tablet containing sitagliptin and metformin is considered appropriate for a patient inadequately controlled on sitagliptin alone, the recommended starting dose of Sitagliptin and Metformin Hydrochloride Tablets is 50mg sitagliptin/

500mg metformin hydrochloride twice daily. Patients with inadequate control on this dose can be titrated up to 50mg sitagliptin/ 1000mg metformin hydrochloride twice daily. Patients taking Sitagliptin monotherapy dose-adjusted for renal impairment should not be switched to Sitagliptin and Metformin Hydrochloride Tablets.

Patients switching from coadministration of sitagliptin and metformin:
For patients switching from sitagliptin coadministered with metformin, Sitagliptin and Metformin Hydrochloride Tablets may be initiated at the dose of sitagliptin and metformin already being taken.

Patients inadequately controlled on dual combination therapy with any two of the following three antihyperglycaemic agents: sitagliptin, metformin or a sulfonylurea:
If therapy with a combination tablet containing sitagliptin and metformin is considered appropriate in this setting, the usual starting dose of Sitagliptin and Metformin Hydrochloride Tablets should provide sitagliptin dosed as 50mg twice daily (100mg total daily dose). In determining the starting dose of the metformin component, the patient's level of glycaemic control and current dose (if any) of metformin should be considered. Gradual dose escalation to reduce the gastrointestinal (GI) side effect associated with metformin should be considered. Patients currently on or initiating a sulfonylurea may require lower sulfonylurea doses to reduce the risk of hypoglycemia.

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

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

No studies have been performed specifically examining the safety and efficacy of Sitagliptin and Metformin Hydrochloride Tablets in patients previously treated with other oral antihyperglycaemia agents and switched to Sitagliptin and Metformin Hydrochloride Tablets. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycaemic control can occur.
Renal impairment

An eGFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an 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 the risk of lactic acidosis should be reviewed before considering initiation of metformin in patients with eGFR <60 ml/min/1.73 m^2.

If no adequate strength of Sitagliptin and Metformin Hydrochloride Tablets is available, individual monocomponents should be used instead of the fixed dose combination.

eGFR mL/min	Metformin	Sitagliptin
60-89	Maximum daily dose is 3,000 mg. Dose reduction may be considered in relation to declining renal function.	Maximum daily dose is 100 mg.
45-59	Maximum daily dose is 2,000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 100 mg.
30-44	Maximum daily dose is 1,000 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.

4.3 Contraindications

Sitagliptin and Metformin Hydrochloride Tablets is contraindicated in patients with:

1. Severe renal impairment (eGFR <30 mL/min/1.73m^2) (see PRECAUTIONS , Monitoring of renal function).
2. Known hypersensitivity to sitagliptin phosphate, metformin hydrochloride or any other component of Sitagliptin and Metformin Hydrochloride Tablets (see PRECAUTIONS, Sitagliptin phosphate, Hypersensitivity Reactions and SIDE EFFECTS, Postmarketing Experience).
3. Acute or chronic metabolic acidosis, including lactic acidosis, diabetic ketoacidosis with or without coma.

Sitagliptin and Metformin Hydrochloride Tablets should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because the use of such products may result in acute alteration of renal function (see PRECAUTIONS; Metformin hydrochloride).

4.4 Special warnings and precautions for use

Sitagliptin and Metformin Hydrochloride Tablets 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 hemorrhagic or necrotizing pancreatitis (see SIDE EFFECTS), in patients taking

sitagliptin. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of sitagliptin. If pancreatitis is suspected, Sitagliptin and Metformin Hydrochloride Tablets 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 and Metformin Hydrochloride Tablets is contraindicated in severe renal impairment, patients with an eGFR < 30 mL/min/1.73 m^2 (see DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS and PRECAUTIONS, Metformin hydrochloride, Lactic acidosis).

Before initiation of therapy with Sitagliptin and Metformin Hydrochloride Tablets 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 and Metformin Hydrochloride Tablets discontinued if evidence of renal impairment is present.

Hypoglycemia in Combination with a Sulfonylurea or with Insulin: As is typical with other antihyperglycemic agents, hypoglycemia has been observed when sitagliptin and metformin were used in combination with insulin or a sulfonylurea (see SIDE EFFECTS). Therefore, to reduce the risk of sulfonylurea- or insulin-induced hypoglycemia, a lower dose of sulfonylurea or insulin may be considered (see DOSAGE AND ADMINISTRATION).

Sitagliptin Phosphate

Hypoglycemia in Combination with a Sulfonylurea or with Insulin: In clinical trials of sitagliptin as monotherapy and as part of combination therapy with agents not known to cause hypoglycemia (i.e., metformin or a PPARγ agonist (thiazolidinedione), rates of hypoglycemia reported with sitagliptin were similar to rates in patients taking placebo. As typical with other antihyperglycemic agents, hypoglycemia has been observed when sitagliptin was used in combination with insulin or a sulfonylurea (see **SIDE EFFECTS**). Therefore, to reduce the risk of sulfonylurea- or insulin-induced hypoglycemia, a lower dose of sulfonylurea or insulin may be considered (see **DOSAGE AND ADMINISTRATION**).

Hypersensitivity Reactions: There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of Sitagliptin and Metformin Hydrochloride Tablets. 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 and Metformin Hydrochloride Tablets, assess for other potential causes for the event, and institute

alternative treatment for diabetes. (See CONTRAINDICATIONS and SIDE EFFECTS, Postmarketing Experience.)

Bullous Pemphigoid: Postmarketing cases of bullous pemphigoid requiring hospitalization 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 and Metformin Hydrochloride Tablets. If bullous pemphigoid is suspected, Sitagliptin and Metformin Hydrochloride Tablets should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Severe and Disabling Arthralgia: There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

Metformin hydrochloride

Lactic Acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with Sitagliptin and Metformin Hydrochloride Tablets (sitagliptin phosphate/metformin HCl); 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 hypoxemia. Lactic acidosis is characterized 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 µg/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 DOSAGE AND ADMINISTRATION, Recommendations for use in renal impairment). 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 hypoxemia, 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. In addition, metformin should be promptly withheld in the presence of any condition associated with

hypoxemia, 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 stabilized 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 ketonemia).

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 dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery (see CONTRAINDICATIONS).

Hypoglycemia: Hypoglycemia 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 hypoglycemic effects. Hypoglycemia may be difficult to recognize 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 hemodynamic change or may interfere with the disposition of metformin, such as cationic

drugs that are eliminated by renal tubular secretion (see DRUG INTERACTIONS, Metformin hydrochloride), should be used with caution.

Radiologic 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 associated with lactic acidosis in patients receiving metformin (see CONTRAINDICATIONS). Therefore, in patients with an eGFR $\geq$ 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 and Metformin Hydrochloride Tablets 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 DOSAGE AND ADMINISTRATION).

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 Hydrochloride Tablets therapy, the drug should be promptly discontinued.

Surgical procedures: Use of Sitagliptin and Metformin Hydrochloride Tablets 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 DOSAGE AND ADMINISTRATION).

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 and Metformin Hydrochloride Tablets.

Impaired hepatic function: Since impaired hepatic function has been associated with some cases of lactic acidosis, Sitagliptin and Metformin Hydrochloride Tablets should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} levels:

Metformin may reduce vitamin B_{12} serum levels. The risk of low vitamin B_{12} levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B_{12} deficiency. In case of suspicion of vitamin B_{12}deficiency (such as anemia or neuropathy), vitamin B_{12} serum levels should be monitored. Periodic vitamin B_{12} monitoring could be necessary in patients with risk factors for vitamin B_{12} deficiency. Metformin therapy should be continued for as long as it is tolerated and not contraindicated and appropriate corrective treatment for vitamin B_{12} deficiency provided in line with current clinical guidelines.

Change in clinical status of patients with previously controlled type 2 diabetes: A patient with type 2 diabetes previously well controlled on Sitagliptin and Metformin Hydrochloride Tablets 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 and Metformin Hydrochloride Tablets must be stopped immediately and other appropriate corrective measures initiated.

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 Hydrochloride Tablets and temporarily administer insulin. Sitagliptin and Metformin Hydrochloride Tablets may be reinstituted after the acute episode is resolved.

4.5 Interaction with other medicinal products and other forms of interaction

Sitagliptin and metformin
Coadministration 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 and Metformin Hydrochloride Tablets have not been performed; however, such studies have been conducted with the individual components of Sitagliptin and Metformin Hydrochloride Tablets, Sitagliptin and Metformin.

Sitagliptin phosphate
In drug interaction studies, sitagliptin did not have clinically meaningful effects on the pharmacokinetics of the following: metformin, rosiglitazone, glyburide, simvastatin, warfarin, and oral contraceptives. Based on these data, sitagliptin does not inhibit CYP isozymes CYP3A4, 2C8, or 2C9. Based on in vitro data, sitagliptin is also not expected to inhibit CYP2D6, 1A2, 2C19 or 2B6 or to induce CYP3A4.

Population pharmacokinetic analyses have been conducted in patients with type 2 diabetes. Concomitant medications did not have a clinically meaningful effect on sitagliptin pharmacokinetics. Medications 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).

There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (C_{max}, 18%) of digoxin with the coadministration of sitagliptin. These increases are not considered to be clinically meaningful. Patients receiving digoxin should be monitored appropriately. The AUC and C_{max} of sitagliptin were increased

approximately 29% and 68%, respectively, in subjects with coadministration of a single 100-mg oral dose of JANUVIA™ and a single 600-mg oral dose of cyclosporine, a potent probe inhibitor of p-glycoprotein. The observed changes in Sitagliptin pharmacokinetics are not considered to be clinically meaningful.

Metformin hydrochloride

Glyburide: In a single-dose interaction study in type 2 diabetes patients, coadministration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

Furosemide: A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Furosemide 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 furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

Nifedipine: A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine 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 hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving Sitagliptin and Metformin Hydrochloride Tablets the patient should be closely observed to maintain adequate glycemic control.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when coadministered 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

There are no adequate and well-controlled studies in pregnant women with Sitagliptin and Metformin Hydrochloride Tablets or its individual components; therefore, the safety of Sitagliptin and Metformin Hydrochloride Tablets in pregnant women is not known. Sitagliptin and Metformin Hydrochloride Tablets, like other oral antihyperglycemic agents, is not recommended for use in pregnancy.

No animal studies have been conducted with the combined products in Sitagliptin and Metformin Hydrochloride Tablets to evaluate effects on reproduction. The following data are based on findings in studies performed with sitagliptin or metformin individually.

Sitagliptin phosphate
Sitagliptin was not teratogenic in rats at oral doses up to 250 mg/kg or in rabbits given up to 125 mg/kg during organogenesis (up to 32 and 22 times, respectively, the human exposure based on the recommended daily adult human dose of 100 mg/day). In rats, a slight increase in the incidence of fetal rib malformations (absent, hypoplastic and wavy ribs) was observed 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/day).
Slight decreases in mean preweaning body weights of both sexes and postweaning body weight gains of males were observed in the offspring of rats given oral dose of 1000 mg/kg/day. However, animal reproduction studies are not always predictive of the human response.

Metformin hydrochloride
Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 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 fetal concentrations demonstrated a partial placental barrier to metformin.

Nursing Mothers

No studies in lactating animals have been conducted with the combined components of Sitagliptin and Metformin Hydrochloride Tablets. In studies performed with the individual components, both sitagliptin and metformin are secreted in the milk of lactating rats. It is

not known whether sitagliptin is excreted in human milk. Therefore, Sitagliptin and Metformin Hydrochloride Tablets should not be used by a woman who is nursing.

4.7 Effects on ability to drive and use machines

Information is not available.

4.8 Undesirable effects

In placebo-controlled clinical trials, in patients with type 2 diabetes mellitus, the combination of sitagliptin and metformin was generally well tolerated. The overall incidence of side effects reported in patients receiving the combination of sitagliptin and metformin was similar to that reported in patients receiving the combination of placebo and metformin.

Combination Therapy with Sitagliptin and Metformin

Initial Therapy

In a 24-week placebo-controlled factorial study of initial therapy with sitagliptin 50 mg twice daily in combination with metformin at 500 or 1000 mg twice daily, the drugrelated adverse reactions reported in ≥1% of patients receiving combination therapy (and greater than in patients receiving placebo) are shown in Table 1.

Table 1
Initial Therapy with Combination of Sitagliptin and Metformin:
Drug-Related Adverse Reactions Reported in ≥ 1% of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Placebo)†

	Number of Patients (%)			
	Placebo	Sitagliptin 100 mg q.d.	Metformin 500 or 1000 mg b.i.d. † †	Sitagliptin 50 mg b.i.d. + Metformin 500 or 1000 mg b.i.d. † †
	N = 176	N = 179	N = 364	N = 372
Diarrhea	2 (1.1)	0 (0.0)	12 (3.3)	13 (3.5)
Nausea	1 (0.6)	0 (0.0)	9 (2.5)	6 (1.6)
Dyspepsia	0 (0.0)	0 (0.0)	4 (1.1)	5 (1.3)
Flatulence	0 (0.0)	0 (0.0)	2 (0.5)	5 (1.3)
Vomiting	0 (0.0)	0 (0.0)	1 (0.3)	4 (1.1)
Headache	0 (0.0)	1 (0.6)	4 (1.1)	5 (1.3)
Hypoglycemia	0 (0.0)	1 (0.6)	2 (0.5)	4 (1.1)

† Intent-to-treat population

† † Data pooled for the patients given the lower and higher doses of metformin.

Add-on Combination Therapy to Metformin

In a 24-week placebo-controlled study of sitagliptin added to ongoing metformin therapy, 464 patients on metformin were treated with sitagliptin 100 mg once daily and 237 patients were given placebo with metformin. The only drug-related adverse reaction reported that occurred with an incidence of ≥ 1% and higher than placebo in patients receiving sitagliptin

and metformin was nausea (100 mg sitagliptin and metformin; 1.1%, placebo and metformin, 0.4%).

Hypoglycemia and Gastrointestinal Adverse Experiences

In the placebo-controlled studies of combination therapy with sitagliptin and metformin, the incidence of hypoglycemia (regardless of investigator assessment of causality) reported in patients treated with the combination of sitagliptin and metformin was similar to that reported for patients treated with metformin and placebo. 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 2.

Table 2
Hypoglycemia and Pre-specified Gastrointestinal Intestinal Adverse Experiences (Regardless of Investigator Assessment of Causality) Reported in Patients Receiving Combination Therapy†

	Number of Patients (%)					
	Study of Sitagliptin and Metformin as Initial Therapy				Study of Sitagliptin as Add-on to Metformin	
	Placebo	Sitagliptin 100 mg q.d.	etformin 500 or 1000 mg b.i.d. † †	Sitagliptin 50 mg b.i.d. + Metformin 500 or 1000 mg b.i.d. † †	Placebo and Metformin ≥ 1500 mg daily	Sitagliptin 100 mg q.d. and Metformin ≥ 1500 mg daily
	N = 176	N = 179	N = 364	N = 372	N= 237	N= 464
Hypoglycemia	1 (0.6)	1 (0.6)	3 (0.8)	6 (1.6)	5 (2.1)	6 (1.3)
Diarrhea	7 (4.0)	5 (2.8)	28 (7.7)	28 (7.5)	6 (2.5)	11 (2.4)
Nausea	2 (1.1)	2 (1.1)	20 (5.5)	18 (4.8)	2 (0.8)	6 (1.3)
Vomiting	1 (0.6)	0 (0.0)	2 (0.5)	8 (2.1)	2 (0.8)	5 (1.1)
Abdominal Pain†	4 (2.3)	6 (3.4)	14 (3.8)	11(3.0)	9 (3.8)	10 (2.2)

† In the study of initial therapy, Abdominal Discomfort was included with Abdominal Pain
† † Data pooled for the patients given the lower and higher doses of metformin.

In all studies, adverse experiences of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required.

Sitagliptin in Combination with Metformin and a Sulfonylurea

In a 24-week placebo-controlled study of sitagliptin 100 mg daily added to ongoing combination treatment with glimepiride ≥ 4 mg daily and metformin ≥ 1500 mg daily, the drug-related adverse reactions reported in ≥1% of patients treated with Sitagliptin (N=116) and more commonly than in patients treated with placebo (N=113) were hypoglycemia (sitagliptin, 13.8%; placebo, 0.9%) and constipation (1.7%, 0.0%).

Sitagliptin in Combination with Metformin and a PPARγ Agonist

In a placebo-controlled study of sitagliptin 100 mg daily added to ongoing combination treatment with metformin and rosiglitazone, the drug-related adverse reactions reported

through the primary time point at Week 18 in ≥ 1% of patients treated with Sitagliptin (N=170) and more commonly than in patients treated with placebo (N=92) were: headache (sitagliptin, 2.4%; placebo, 0.0%), diarrhea (1.8%, 1.1%), nausea (1.2%, 1.1%), hypoglycemia (1.2%, 0.0%), and vomiting (1.2%, 0.0%). Through Week 54, the drug-related adverse reactions reported in ≥ 1% of patients treated with sitagliptin and more commonly than in patients treated with placebo were: headache (2.4%, 0.0%), hypoglycemia (2.4%, 0.0%), upper respiratory tract infection (1.8%, 0.0%), nausea (1.2%, 1.1%), cough (1.2%, 0.0%), fungal skin infection (1.2%, 0.0%), peripheral edema (1.2%, 0.0%), and vomiting (1.2%, 0.0%).

Sitagliptin in Combination with Metformin and Insulin
In a 24-week placebo-controlled study of sitagliptin 100 mg added to ongoing combination treatment with metformin ≥ 1500 mg daily and stable-dose insulin, the only drug-related adverse reaction reported in ≥ 1% of patients treated with Sitagliptin (N=229) and more commonly than in patients treated with placebo (N=233) was hypoglycemia (sitagliptin, 10.9%; placebo, 5.2%). In another 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%).

Pancreatitis
In a pooled analysis of 19 double-blind clinical trials that included data from 10,246 patients randomized to receive sitagliptin 100 mg/day (N=5429) or corresponding (active or placebo) control (N=4817), the incidence of non-adjudicated cute pancreatitis events was 0.1 per 100 patient-years in each group (4 patients with an event in 4708 patient-years for sitagliptin and 4 patients with an event in 3942 patient-years for control). See also TECOS Cardiovascular Safety Study, below. (See PRECAUTIONS, Pancreatitis)
With the combination of sitagliptin and metformin, no clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed.

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 following adverse reactions may occur under treatment with metformin. Frequencies are defined as follows: very common ≥ 1/10; common ≥ 1/100 - <1/10; uncommon ≥ 1/1,000 - <1/100; rare ≥ 1/10,000 - <1/1,000; very rare <1/10,000. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

<u>Metabolism and nutrition disorders</u>
Common: Vitamin B_{12} decrease/deficiency (see Precautions)
Very Rare : Lactic acidosis (see Precautions)
<u>Nervous system disorders:</u>
Common: Taste disturbance

Gastrointestinal disorders:
Very common: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders:
Very Rare: Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders:
Very rare: Skin reactions such as erythema, pruritus, urticaria

TECOS Cardiovascular Safety Study
TECOS Cardiovascular 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 HbA_{1c} 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 hypoglycaemia 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 hypoglycaemia 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.

Pediatric population
In a pooled analysis of two placebo-controlled clinical studies with Sitagliptin and Metformin Hydrochloride Tablets and Sitagliptin and Metformin Hydrochloride Tablets Extended Release in pediatric patients aged 10 to 17 years with type 2 diabetes, the drug-related adverse reactions reported through the 54-week treatment period in ≥1% of patients in the Sitagliptin and Metformin Hydrochloride Tablets and Sitagliptin and Metformin Hydrochloride Tablets Extended Release group (N=107) and more commonly than in patients in the Metformin/Metformin XR group (N=113) were diarrhea (Sitagliptin and Metformin Hydrochloride Tablets and Sitagliptin and Metformin Hydrochloride Tablets Extended Release, 2.8%; Metformin/Metformin XR, 0.9%), nausea (2.8%, 0.9%), and hypoglycemia (6.5%, 3.5%).

The profile of side effects was comparable to that observed in adults. There were no clinically relevant differences between the Sitagliptin and Metformin Hydrochloride Tablets and Sitagliptin and Metformin Hydrochloride Tablets Extended Release groups through Week 54 in laboratory safety endpoints, vital signs, indices of adiposity, or growth and development endpoints.

Postmarketing Experience:
Additional adverse reactions have been identified during postmarketing use of Sitagliptin and Metformin Hydrochloride Tablets or sitagliptin, one of the components of Sitagliptin and Metformin Hydrochloride Tablets. These reactions have been reported when Sitagliptin and Metformin Hydrochloride Tablets or sitagliptin have been used alone and/or in combination with other antihyperglycemic 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.

Hypersensitivity reactions, including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome (see CONTRAINDICATIONS and PRECAUTIONS, Sitagliptin phosphate, Hypersensitivity Reactions); acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis (see PRECAUTIONS, Pancreatitis); worsening renal function, including acute renal failure (sometimes requiring dialysis);bullous pemphigoid (see PRECAUTIONS, Bullous Pemphigoid); severe and disabling arthralgia (see PRECAUTIONS, Severe and Disabling Arthralgia); upper respiratory tract infection; nasopharyngitis; constipation; vomiting; headache; myalgia; pain in extremity; back pain; pruritus; thrombocytopenia.

4.9 Overdose

Sitagliptin phosphate
During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were generally well tolerated. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin (see CLINICAL PHARMACOLOGY, Pharmacodynamics, Cardiac Electrophysiology).
There is no experience with doses above 800 mg in clinical studies. In Phase I multipledose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.
In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

Metformin hydrochloride
Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was 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 PRECAUTIONS,

Metformin hydrochloride). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin over dosage 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

Pharmacodynamic

Sitagliptin phosphate

General
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 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 Phase II studies, sitagliptin 50 mg twice daily provided similar glycemic efficacy compared to sitagliptin 100 mg once daily.

In a randomized, placebo-controlled, double-blind, double-dummy, four-period crossover two-day study in healthy adult subjects, the effects on post-meal plasma concentrations of active and total GLP-1 and glucose after coadministration 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 coadministration 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 data are consistent with different mechanisms for the increase in active GLP-1 concentrations.
Results from the study also demonstrated that sitagliptin, but not metformin, enhances active GIP concentrations.
In studies with healthy subjects, sitagliptin did not lower blood glucose or cause hypoglycemia, suggesting that the insulinotropic and glucagon suppressive actions of the drug are glucose dependent.

Effects on blood pressure

In a randomized, placebo-controlled crossover 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), coadministration 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 mmHg, as compared to placebo. Reductions have not been observed in subjects with normal blood pressure.

Cardiac Electrophysiology
In a randomized, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of sitagliptin 100mg 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 obtained 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 was not considered to be clinically significant. At the 800- mg dose, peak sitagliptin plasma concentrations were approximately 11 times higher than the peak concentrations following a 100-mg dose.
In patients with type 2 diabetes administered sitagliptin 100 mg (N=81) or sitagliptin 200 mg (N=63) daily, there were no meaningful changes in QTc interval based on ECG data obtained at the time of expected peak plasma concentration.

Clinical Pharmacology

Mechanism of action

Sitagliptin and Metformin Hydrochloride Tablets combines two antihyperglycemic agents 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 phosphate

Sitagliptin phosphate is a member of a class of oral antihyperglycemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors, which improve glycemic 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 signaling pathways involving cyclic AMP. Treatment with GLP-1 or with DPP-4 inhibitors in animal models of type 2 diabetes has been demonstrated to improve beta cell responsiveness to glucose and stimulate insulin biosynthesis and release. With higher insulin levels, tissue glucose uptake is enhanced. In addition, GLP-1 lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon concentrations, along with higher insulin levels, lead to reduced hepatic glucose production, resulting in a

decrease in blood glucose levels. The effects of GLP-1 and GIP are glucose-dependent. 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 secretion is enhanced as glucose rises above normal concentrations. GLP-1 does not impair the normal glucagon response to hypoglycemia. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyzes the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in a glucose-dependent manner. This glucose dependent mechanism is unlike the mechanism seen with sulfonylureas where insulin is released even when glucose levels are low, which can lead to hypoglycemia in patients with type 2 diabetes and in normal subjects. In patients with type 2 diabetes with hyperglycemia, these changes in insulin and glucagon levels lead to lower hemoglobin A_{1c} (HbA_{1c}) and lower fasting and postprandial glucose concentrations. 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.

Metformin hydrochloride

Mechanism of action
Metformin is an antihyperglycemic 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 antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see PRECAUTIONS, Metformin hydrochloride) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

5.2 Pharmacokinetic properties

The results of a definitive bioequivalence study conducted by Innovator in healthy subjects demonstrated that the JANUMET (sitagliptin/metformin hydrochloride) 50 mg/500 mg and 50 mg/1000 mg combination tablets are bioequivalent to coadministration of corresponding doses of sitagliptin phosphate (JANUVIA™) and metformin hydrochloride as individual tablets.

Because bioequivalence is demonstrated at the lowest and highest combination tablet dose strengths available, bioequivalence is conferred to the (sitagliptin/metformin) 50 mg/850 mg fixed dose combination (FDC) tablet.

Sitagliptin phosphate

Absorption

The absolute bioavailability of sitagliptin is approximately 87%. Coadministration of a high-fat meal with sitagliptin phosphate had no effect on the pharmacokinetics of sitagliptin.

Distribution

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

Metabolism

Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79% of sitagliptin is excreted unchanged in the urine.

Following a [^{14}C] sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

Elimination

Following administration of an oral [^{14}C] sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing. The apparent terminal $t_{1/2}$ following a 100-mg oral dose of sitagliptin was approximately 12.4 hours 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, cyclosporine, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

Metformin hydrochloride

Absorption

The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50-60%. 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 alternation in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown 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

The 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 reached within 24-48 hours and are generally <1 mcg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism

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) nor biliary excretion.

Elimination

Renal clearance is 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 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 approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Characteristics in Patients

Type 2 Diabetes

Sitagliptin phosphate

The pharmacokinetics of sitagliptin in patients with type 2 diabetes are generally similar to those in healthy subjects.

Metformin hydrochloride

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 phosphate

An approximately 2-fold increase in the plasma AUC of sitagliptin was observed 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 observed in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) including patients with end-stage renal disease (ESRD) on hemodialysis, as compared to subjects with normal renal function.

Metformin hydrochloride

In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased (see CONTRAINDICATIONS and PRECAUTIONS).

Hepatic Impairment

Sitagliptin phosphate

In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and C_{max} of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100-mg dose of sitagliptin phosphate. 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 hydrochloride

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

Gender

Sitagliptin phosphate

Gender had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

Metformin hydrochloride

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analyzed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin was comparable in males and females.

Elderly

Sitagliptin phosphate

Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

Metformin hydrochloride

Limited data from controlled pharmacokinetic 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 data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatric

The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in pediatric patients (10 to 17 years of age) with type 2 diabetes. In this population, the dose-adjusted AUC of sitagliptin in plasma was approximately 18% lower compared to adult patients with type 2 diabetes for a 100 mg dose. This is not considered to be a clinically meaningful difference based on the flat PK/PD relationship between the dose of 50 mg and 100 mg in adults.

No studies with sitagliptin have been performed in pediatric patients < 10 years of age.

Race

Sitagliptin phosphate

Race had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data, including subjects of white, Hispanic, black, Asian, and other racial groups.

Metformin hydrochloride

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n= 51), and Hispanics (n=24).

Body Mass Index (BMI)

Sitagliptin phosphate

Body mass index (BMI) had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

5.3 Preclinical safety data

No preclinical data available

6.0 Pharmaceutical particulars

6.1 List of excipients

Croscarmellose Sodium, Talc, Sodium Stearyl Fumarate, Dicalcium Phosphate Anhydrous, Colloidal silicon dioxide, Hypromellose, Isopropyl alcohol, Methylene chloride, Microcrystalline Cellulose, Crospovidone, Povidone, Purified water, Magnesium Stearate

Opadry composition: Hypromellose, Titanium Dioxide, Macrogol, Talc

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

Please refer to the outer carton for the expiry date.

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture.

6.5 Nature and contents of container and special equipment for use, administration or implantation

14 Tablet packed in Alu-Alu blister and such 2 blister in carton along with package insert.

14 Tablet packed in Alu-Alu blister and such 4 blister in carton along with package insert.

6.6 Special precautions for disposal and other handling

Not applicable

7 PRODUCT REGISTRATION HOLDER

Pahang Pharmacy Sdn. Bhd.
Lot 5979, Jalan Teratai,
5 ½ Mile Off Jalan Meru,
41050 Klang, Selangor.
Malaysia

8 MANUFACTURER

Manufactured by:
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