

SITAVIO-M 50mg/500mg
SITAVIO-M 50mg/850mg
SITAVIO-M 50mg/1000mg

Film Coated Tablets

1. NAME OF THE MEDICINAL PRODUCT

SITAVIO-M 50mg/500mg Film Coated Tablets
SITAVIO-M 50mg/850mg Film Coated Tablets
SITAVIO-M 50mg/1000mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SITAVIO-M 50mg/500mg Film Coated Tablets: Each tablet contains 64.25mg of Sitagliptin Phosphate Monohydrate equivalent to 50mg of Sitagliptin and Metformin Hydrochloride 500mg.

SITAVIO-M 50mg/850mg Film Coated Tablets: Each tablet contains 64.25mg of Sitagliptin Phosphate Monohydrate equivalent to 50mg of Sitagliptin and Metformin Hydrochloride 850mg.

SITAVIO-M 50mg/1000mg Film Coated Tablets: Each tablet contains 64.25mg of Sitagliptin Phosphate Monohydrate equivalent to 50mg of Sitagliptin and Metformin Hydrochloride 1000mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film Coated Tablets.

SITAVIO-M 50mg/500mg Film Coated Tablets: Light pink, oblong, biconvex, film-coated tablet, debossed with 'C 37' on one side of tablet and plain on the other side.

SITAVIO-M 50mg/850mg Film Coated Tablets: Pink, oblong, biconvex, film-coated tablet, debossed with 'C 35' on one side of tablet and plain on the other side.

SITAVIO-M 50mg/1000mg Film Coated Tablets: Red, oblong, biconvex, film-coated tablet, debossed with 'C 34' on one side of tablet and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SITAVIO-M 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.

SITAVIO-M 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.

SITAVIO-M 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.

SITAVIO-M is indicated as triple combination therapy with a PPAR γ 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 PPAR γ agonist.

SITAVIO-M 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.

4.2 Posology and method of administration

The dosage of antihyperglycaemic therapy with SITAVIO-M 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.

SITAVIO-M 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 SITAVIO-M should be based on the patient's current regimen. SITAVIO-M 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 SITAVIO-M 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 SITAVIO-M 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 SITAVIO-M.

Patients switching from coadministration of sitagliptin and metformin:

For patients switching from sitagliptin coadministered with metformin, SITAVIO-M 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 SITAVIO-M 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 PPAR γ agonist:

The dose of SITAVIO-M should provide sitagliptin dosed as 50mg twice daily (100mg 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 SITAVIO-M should provide sitagliptin dosed as 50mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When SITAVIO-M is used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycemia.

No studies have been performed specifically examining the safety and efficacy of SITAVIO-M in patients previously treated with other oral antihyperglycaemia agents and switched to SITAVIO-M. 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:

A GFR 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 GFR <60 ml/min.

If no adequate strength of SITAVIO-M is available, individual monocomponents should be used instead of the fixed dose combination.

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

4.3 Contraindications

SITAVIO-M is contraindicated in patients with:

1. Severely reduced kidney function (GFR <30 mL/min)
2. Known hypersensitivity to sitagliptin phosphate, metformin hydrochloride or any other component of SITAVIO-M.
3. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)

SITAVIO-M 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.

4.4 Special warnings and precautions for use

General

SITAVIO-M 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, 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, SITAVIO-M 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. SITAVIO-M is contraindicated in severe renal impairment, patients with an eGFR < 30 mL/min/1.73 m².

Before initiation of therapy with SITAVIO-M 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 SITAVIO-M 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. Therefore, to reduce the risk of sulfonylurea- or insulin-induced hypoglycemia, a lower dose of sulfonylurea or insulin may be considered.

Sitagliptin

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 PPAR γ 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. Therefore, to reduce the risk of sulfonylurea- or insulin-induced hypoglycemia, a lower dose of sulfonylurea or insulin may be considered.

Hypersensitivity Reactions: There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of SITAVIO-M. 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 SITAVIO-M, assess for other potential causes for the event, and institute alternative treatment for diabetes.

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 SITAVIO-M. If bullous pemphigoid is suspected, SITAVIO-M 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

Lactic Acidosis

Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis.

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (<7.35), increased plasma lactate levels (>5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

Renal function: GFR should be assessed before treatment initiation and regularly thereafter. Metformin is contraindicated in patients with GFR <30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function.

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, 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. Therefore, in patients with an eGFR ≥ 30 to <60 mL/min/1.73 m², in patients with a history of hepatic impairment, alcoholism, or heart failure, or in patients who will be administered intra-arterial iodinated contrast, SITAVIO-M 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.

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 SITAVIO-M therapy, the drug should be promptly discontinued.

Surgical procedures: Use of SITAVIO-M 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.

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 SITAVIO-M.

Impaired hepatic function: Since impaired hepatic function has been associated with some cases of lactic acidosis, SITAVIO-M should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B₁₂ levels: Metformin may reduce vitamin B₁₂ serum levels. The risk of low vitamin B₁₂ levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B₁₂ deficiency. In case of suspicion of vitamin B₁₂ deficiency (such as anemia or neuropathy), vitamin B₁₂ serum levels should be monitored. Periodic vitamin B₁₂ monitoring could be necessary in patients with risk factors for vitamin B₁₂ deficiency. Metformin therapy should be continued for as long as it is tolerated and not contraindicated and appropriate corrective treatment for vitamin B₁₂ 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 SITAVIO-M 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, SITAVIO-M 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 SITAVIO-M and temporarily administer insulin. SITAVIO-M may be reinstituted after the acute episode is resolved.

Sodium: This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

SITAVIO-M

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 SITAVIO-M have not been performed; however, such studies have been conducted with the individual components of SITAVIO-M, sitagliptin and metformin.

Sitagliptin

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 sitagliptin 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

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 SITAVIO-M 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

Pregnancy

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

A limited amount of data suggests the use of metformin in pregnant women is not associated with an increased risk of congenital malformations.

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

Breast-feeding

No studies in lactating animals have been conducted with the combined active substances of this medicinal product. In studies performed with the individual active substances, both sitagliptin and metformin are excreted in the milk of lactating rats. Metformin is excreted in human milk in small amounts. It is not known whether sitagliptin is excreted in human milk. SITAVIO-M must therefore not be used in women who are breast-feeding.

Fertility

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

4.7 Effects on ability to drive and use machines

SITAVIO-M has no or negligible influence on the ability to drive and use machines. However, when driving or using machines, it should be taken into account that dizziness and somnolence have been reported with sitagliptin.

In addition, patients should be alerted to the risk of hypoglycaemia when SITAVIO-M is used in combination with a sulphonylurea or with insulin.

4.8 Undesirable effects

Summary of the safety profile

Serious adverse reactions including pancreatitis and hypersensitivity reactions have been reported. Hypoglycaemia has been reported in combination with sulphonylurea (13.8 %) and insulin (10.9 %).

Sitagliptin and metformin

Tabulated list of adverse reactions

Adverse reactions are listed below as MedDRA preferred term by system organ class and absolute frequency.

Adverse reaction	Frequency of adverse reaction
Blood and lymphatic system disorders	
thrombocytopenia	Rare
Immune system disorders	
hypersensitivity reactions including anaphylactic responses*	Frequency not known
Metabolism and nutrition disorders	
hypoglycaemia	Common
Vitamin B12 decrease/deficiency	Common
Nervous system disorders	
somnolence	Uncommon
Respiratory, thoracic and mediastinal disorders	
interstitial lung disease*	Frequency not known
Gastrointestinal disorders	
diarrhoea	Uncommon
nausea	Common
flatulence	Common
constipation	Uncommon
upper abdominal pain	Uncommon
vomiting	Common
acute pancreatitis*	Frequency not known
fatal and non-fatal haemorrhagic and necrotizing pancreatitis*	Frequency not known
Skin and subcutaneous tissue disorders	
pruritus*	Uncommon
angioedema*	Frequency not known
rash*	Frequency not known
urticaria*	Frequency not known
cutaneous vasculitis*	Frequency not known
exfoliative skin conditions including Stevens-Johnson syndrome*	Frequency not known
bullous pemphigoid*	Frequency not known
Musculoskeletal and connective tissue disorders	
arthralgia*	Frequency not known
myalgia*	Frequency not known
pain in extremity*	Frequency not known
back pain*	Frequency not known
arthropathy*	Frequency not known
Renal and urinary disorders	
impaired renal function*	Frequency not known
acute renal failure*	Frequency not known

*Adverse reactions were identified through post-marketing surveillance

Description of selected adverse reactions

Some adverse reactions were observed more frequently in studies of combination use of sitagliptin and metformin with other anti-diabetic medicinal products than in studies of sitagliptin and metformin

alone. These included hypoglycaemia (frequency very common with sulphonylurea or insulin), constipation (common with sulphonylurea), peripheral oedema (common with pioglitazone), and headache and dry mouth (uncommon with insulin).

Sitagliptin

In monotherapy studies of sitagliptin 100 mg once daily alone compared to placebo, adverse reactions reported were headache, hypoglycaemia, constipation, and dizziness.

Among these patients, adverse events reported regardless of causal relationship to medicinal product occurring in at least 5 % included upper respiratory tract infection and nasopharyngitis. In addition, osteoarthritis and pain in extremity were reported with frequency uncommon.

Metformin

Gastrointestinal symptoms were reported very commonly in clinical studies and post-marketing use of metformin. Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases. Additional adverse reactions associated with metformin include metallic taste (common); lactic acidosis, liver function disorders, hepatitis, urticaria, erythema, and pruritus (very rare). Frequency categories are based on information available from metformin Summary of Product Characteristics available in the EU.

Paediatric population

In study with Sitagliptin/Metformin in paediatric patients with type 2 diabetes mellitus aged 10 to 17 years, the profile of adverse reactions was generally comparable to that observed in adults. In paediatric patients on or not on background insulin, sitagliptin was associated with an increased risk of hypoglycaemia.

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 m²), and 7,339 patients treated with placebo in the intention-to-treat population. Both treatments were added to usual care targeting regional standards for HbA1c 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 sulphonylurea 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 sulphonylurea 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.

4.9 Overdose

During studies in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

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

In clinical studies, approximately 13.5 % of the dose was removed over a 3- to 4-hour haemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if

sitagliptin is dialysable by peritoneal dialysis.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Sitagliptin

Mechanism of action

Sitagliptin phosphate is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production.

When blood glucose levels are low, insulin release is not enhanced and glucagon secretion is not suppressed. Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations. Sitagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulphonylureas or meglitinides, biguanides, peroxisome proliferator-activated receptor gamma (PPAR γ) agonists, alpha-glucosidase inhibitors, and amylin analogues.

Metformin

Mechanism of action

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

Metformin may act via three mechanisms:

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

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

5.2 Pharmacokinetic properties

Sitagliptin/Metformin

A bioequivalence study in healthy subjects demonstrated that the Sitagliptin/Metformin combination tablets are bioequivalent to co-administration of sitagliptin phosphate and metformin hydrochloride as

individual tablets.

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

Sitagliptin

Absorption

Following oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8.52 $\mu\text{M}\cdot\text{hr}$, C_{max} was 950nM. The absolute bioavailability of sitagliptin is approximately 87 %. Since co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food.

Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for C_{max} and C_{24hr} (C_{max} increased in a greater than dose-proportional manner and C_{24hr} increased in a less than dose-proportional manner).

Distribution

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

Biotransformation

Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79% of sitagliptin is excreted unchanged in the urine. Following a [^{14}C]sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8. *In vitro* data showed that sitagliptin is not an inhibitor of CYP isoenzymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4 and CYP1A2.

Elimination

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

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin. Sitagliptin is not a substrate for OCT2 or OAT1 or PEPT1/2 transporters.

In vitro, sitagliptin did not inhibit OAT3 ($\text{IC}_{50}=160 \mu\text{M}$) or p-glycoprotein (up to 250 μM) mediated transport at therapeutically relevant plasma concentrations. In a study sitagliptin had a small effect on plasma digoxin concentrations indicating that sitagliptin may be a mild inhibitor of p-glycoprotein.

Characteristics in Patients

Type 2 Diabetes

The pharmacokinetics of sitagliptin were generally similar in healthy subjects and in patients with type 2 diabetes.

Renal Impairment

A study was conducted to evaluate the pharmacokinetics of a reduced dose of sitagliptin (50 mg) in patients with varying degrees of chronic renal impairment compared to normal healthy control subjects. The study included patients with mild, moderate, and severe renal impairment, as well as patients with ESRD on haemodialysis. In addition, the effects of renal impairment on sitagliptin pharmacokinetics in patients with type 2 diabetes and mild, moderate, or severe renal impairment (including ESRD) were assessed using population pharmacokinetic analyses.

Compared to normal healthy control subjects, plasma AUC of sitagliptin was increased by approximately 1.2-fold and 1.6-fold in patients with mild renal impairment ($\text{GFR} \geq 60$ to < 90 mL/min) and patients with moderate renal impairment ($\text{GFR} \geq 45$ to < 60 mL/min), respectively. Because increases of this magnitude are not clinically relevant, dose adjustment in these patients is not necessary.

Plasma AUC of sitagliptin was increased approximately 2-fold in patients with moderate renal impairment ($\text{GFR} \geq 30$ to < 45 mL/min), and approximately 4-fold in patients with severe renal impairment ($\text{GFR} < 30$ mL/min), including patients with ESRD on hemodialysis. Sitagliptin was modestly removed by haemodialysis (13.5 % over a 3- to 4-hour haemodialysis session starting 4 hours post-dose).

Hepatic Impairment

No dose adjustment for sitagliptin is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score ≤ 9). There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score > 9). However, because sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetics of sitagliptin.

Elderly

No dose adjustment is required based on age. Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis data. Elderly subjects (65 to 80 years) had approximately 19 % higher plasma concentrations of sitagliptin compared to younger subjects.

Paediatric population

The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in paediatric patients (10 to 17 years of age) with type 2 diabetes. In this population, the dose adjusted AUC of sitagliptin in plasma was approximately 18 % lower compared to adult patients with type 2 diabetes for a 100 mg dose. No studies with sitagliptin have been performed in paediatric patients < 10 years of age.

Other patient characteristics

No dose adjustment is necessary based on gender, race, or body mass index (BMI).

Metformin

Absorption

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

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 $\mu\text{g/mL}$. In studies, maximum metformin plasma levels (C_{max}) did not exceed 5 $\mu\text{g/mL}$, even at maximum doses.

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

decrease is unknown.

Distribution

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

Biotransformation

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

Elimination

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline Cellulose, Sodium Lauryl Sulfate, Povidone, Isopropyl Alcohol, Sodium Stearyl Fumarate.

Film-coated:

Opadry II Complete Film Coating System 85F540226 Pink (SITAVIO-M 50mg/500mg), Opadry II Complete Film Coating System 85F94182 Pink (SITAVIO-M 50mg/850mg), Opadry II Complete Film Coating System 85F15464 Red (SITAVIO-M 50mg/1000mg)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to the expiry date on the product labels.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Alu (OPA/Alu/PVC)/Alu blisters pack in the outer carton of 1 x 10's, 3 x 10's, 6 x 10's, 10 x 10's, 50 x 10's, 100 x 10's. Not all packs sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MANUFACTURER

Manufactured by:

Novugen Pharma Sdn. Bhd.
No. 27, Jalan Lengkuk Teknologi 2,
Taman Teknologi Enstek Fasa 1,
71760 Bandar Baru Enstek,
Negeri Sembilan, Malaysia.

Product Registration Holder:

Novugen Pharma Sdn. Bhd.
No. 3, Jalan Jururancang U1/21,
Hicom Glenmarie Industrial Park
40150 Shah Alam, Selangor, Malaysia.

8 DATE OF REVISION

01/08/2024

Package insert is drafted in Times New Roman with font size of 11, subject to change based on any other legible font and font size.
