Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

SITAGLIPTIN/METFORMIN 50/500 SUN PHARMA (Film coated tablets)

SITAGLIPTIN/METFORMIN 50/850 SUN PHARMA (Film coated tablets)

SITAGLIPTIN/METFORMIN 50/1000 SUN PHARMA (Film coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SITAGLIPTIN/METFORMIN 50/500 SUN PHARMA

Each film coated tablet contains:

Sitagliptin Fumarate equivalent to Sitagliptin 50 mg and Metformin Hydrochloride 500 mg

Sugar free

SITAGLIPTIN/METFORMIN 50/850 SUN PHARMA

Each film coated tablet contains:

Sitagliptin Fumarate equivalent to Sitagliptin 50 mg and Metformin Hydrochloride 850 mg

Sugar free

SITAGLIPTIN/METFORMIN 50/1000 SUN PHARMA

Each film coated tablet contains:

Sitagliptin Fumarate equivalent to Sitagliptin 50 mg and Metformin Hydrochloride 1000 mg

Sugar free

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

3. PHARMACEUTICAL FORM

Film coated tablets

SITAGLIPTIN/METFORMIN 50/500 SUN PHARMA

Light pink to pink, Capsule shaped film-coated tablets debossed with “SC5” on one side.

SITAGLIPTIN/METFORMIN 50/850 SUN PHARMA

Pink, Capsule shaped film-coated tablets debossed with “SC1” on one side.

SITAGLIPTIN/METFORMIN 50/1000 SUN PHARMA

Brown to Reddish brown, Capsule shaped film-coated tablets debossed with “SC7” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

SITAGLIPTIN/METFORMIN 50/50; 50/850; 50/1000 SUN PHARMA is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus, already being treated with sitagliptin and metformin given separately.

SITAGLIPTIN/METFORMIN 50/50; 50/850; 50/1000 SUN PHARMA is also indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in patients with type 2 diabetes mellitus, inadequately controlled with any two of the three medicines: Metformin, sitagliptin or a sulphonylurea.

4.2 Posology and Method of Administration

General

The dosage of antihyperglycaemic therapy with sitagliptin and metformin should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin.

The combination of sitagliptin and metformin should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects associated with metformin.

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

Dosing Recommendations

The starting dose of sitagliptin and metformin should be based on the patient's current regimen. The combination of Sitagliptin and metformin should be given twice daily with meals. The following doses are available:

50 mg sitagliptin/500 mg metformin hydrochloride

50 mg sitagliptin/850 mg metformin hydrochloride

50 mg sitagliptin/1 000 mg metformin hydrochloride

For patients switching from co-administration of sitagliptin and metformin

For patients switching from co-administration of sitagliptin and metformin, **SITAGLIPTIN/METFORMIN 50/50; 50/850; 50/1000 SUN PHARMA** may be initiated at the dose of sitagliptin and metformin already being taken.

For patients inadequately controlled on dual combination therapy with any two of the following three antihyperglycaemic medicines: Sitagliptin, metformin or a sulphonylurea

The usual starting dose of sitagliptin and metformin should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose). In determining the starting dose of the metformin component, the patient's level of glycaemic control and current dose of metformin should be considered. Gradual dose escalation to reduce the gastrointestinal (GI) side effects associated with metformin should be considered. Patients currently on or initiating a sulphonylurea may require lower sulphonylurea doses to reduce the risk of sulphonylurea-induced hypoglycaemia (see **section 4.8**).

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

Special Populations

Patients with Renal Insufficiency

Combination of sitagliptin and metformin should not be used in patients with renal failure or renal dysfunction e.g. serum creatinine levels ≥ 133 micromol/l [males], ≥ 124 micromol/l [females] or abnormal creatinine clearance (see **section 4.3**).

Elderly

As metformin and sitagliptin has been reported to be excreted by the kidneys, sitagliptin/metformin combination should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly (see **section 4.8** and **4.4)**

Paediatric Population

Combination of sitagliptin and metformin is not recommended for use in children below 18 years of age due to lack of data on its safety and efficacy in this population.

4.3 Contraindications

Sitagliptin/metformin hydrochloride combination is contraindicated in patients with:

- Known hypersensitivity to sitagliptin, metformin hydrochloride or any other component of **SITAGLIPTIN/METFORMIN 50/50; 50/850; 50/1000 SUN PHARMA** (see **section 4.4** and **4.8)**.
- Renal disease or renal dysfunction e.g. as suggested by serum creatinine levels ≥ 133 micromol/l [males], ≥ 124 micromol/l [females], or abnormal creatinine clearance which may

also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction and septicaemia.

- Acute or chronic metabolic acidosis including diabetic ketoacidosis, with or without coma.
- acute or chronic disease which may cause tissue hypoxia such as:

– cardiac or respiratory failure,

– recent myocardial infarction,

– shock;

- acute conditions with the potential to alter renal function such as:

- dehydration,
- severe infection,
- shock

- hepatic impairment;
- acute alcohol intoxication, alcoholism
- breast-feeding.
- Severe renal failure (GFR < 30 mL/min) (see section 4.4)
- Diabetic pre-coma

The combination of sitagliptin and metformin 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 section 4.4** and **4.8).**

A history of severe hypersensitivity reaction, such as anaphylaxis or angioedema to the combination of sitagliptin and metformin or any other gliptins (DPP-4).

4.4 Special warnings and precautions for use

Hypersensitivity Reactions: There have been post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of SITAGLIPTIN/METFORMIN 50/50; 50/850; 50/1000 SUN PHARMA. These reactions include anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome. 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 combination of sitagliptin and metformin immediately, and institute an alternative class of medicines for treatment for diabetes (see section 4.3 and **4.8).**

Pancreatitis

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

Use in the elderly

As metformin and sitagliptin are excreted by the kidneys, combination of sitagliptin and metformin should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly **(see section 4.8).**

Special Precautions

The combination of sitagliptin and metformin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Monitoring of renal function: Metformin and sitagliptin are known to be substantially excreted by the kidneys. The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive the combination of sitagliptin and metformin. In patients with advanced age, the combination of sitagliptin and metformin should be carefully titrated to establish the minimum dose for adequate glycaemic effect, because aging can be associated with reduced renal function. In elderly patients, particularly those 80 years of age or older, renal function should be monitored regularly.

Before initiation of therapy with the combination of sitagliptin /metformin and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and the combination of sitagliptin and metformin is contraindicated in patients with GFR < 30 mL/min and should be discontinued if evidence of renal impairment is present.

Bullous pemphigoid

There have been post-marketing reports of bullous pemphigoid in patients taking DPP-4 inhibitors including sitagliptin. If bullous pemphigoid is suspected, sitagliptin/metformin should be discontinued.

Surgery

Sitagliptin/metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Hypoglycaemia in combination with a sulphonylurea: When sitagliptin, a component of **SITAGLIPTIN/METFORMIN 50/50; 50/850; 50/1000 SUN PHARMA** was used in combination with metformin and a sulphonylurea, a medication known to cause hypoglycaemia, the incidence of sulphonylurea-induced hypoglycaemia was reported to increase over that of placebo in combination with metformin and a sulphonylurea. Therefore, to reduce the risk of sulphonylurea-induced hypoglycaemia, a lower dose of sulphonylurea may be considered (see **section 4.2**). The use of sitagliptin/metformin in combination with insulin has not been reported.

Sitagliptin

Hypoglycaemia in combination with a sulphonylurea: In reported clinical trials of sitagliptin as monotherapy and as part of combination therapy with medicines not known to cause hypoglycaemia (i.e. metformin or pioglitazone), rates of hypoglycaemia reported with sitagliptin

were similar to rates in patients taking placebo. As typical with other antihyperglycaemic medicines used in combination with a sulphonylurea, when sitagliptin was used in combination with a sulphonylurea, a medication known to cause hypoglycaemia, the incidence of sulphonylurea-induced hypoglycaemia has been reported to increase over that of placebo. Therefore, to reduce the risk of sulphonylurea-induced hypoglycaemia, a lower dose of sulphonylurea may be considered (see **section 4.2**). The use of sitagliptin in combination with insulin has not been adequately reported.

Metformin hydrochloride

Lactic acidosis: Lactic acidosis is a rare, but serious metabolic complication that can occur due to metformin accumulation during treatment with sitagliptin/metformin hydrochloride combination; when it occurs it is fatal in approximately 50 % of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus and whenever there is significant tissue hypoperfusion and hypoxaemia. Lactic acidosis is characterised by elevated blood lactate levels (> 5 mmol/litre), 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 greater than 5 mcg/ml are generally reported.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1 000 patient-years, with approximately 0.015 fatal cases/1 000 patient-years). In more than 20 000 patient-years exposure to metformin in reported clinical trials,

there has been 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. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxaemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin, and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients 80 years of age or older, unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis.

In addition, metformin should be promptly with held in the presence of any condition associated with hypoxaemia, dehydration or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radio contrast study and for any surgical procedure.

The onset of lactic acidosis often is subtle, and accompanied only by non-specific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence and non-specific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's medical practitioner must be aware of the possible importance of such symptoms and the patient should be instructed to notify the medical practitioner immediately if they occur. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels and even blood metformin levels may be useful. Once a patient is stabilised on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be medicine 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/litre in patients taking metformin, do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity or technical problems in sample handling.
Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonaemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the medicine should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialysable

(with a clearance of up to 170 ml/min under good haemodynamic conditions), prompt haemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery (see **section 4.3).**

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

Use of concomitant medications that may affect renal function or metformin disposition:
Concomitant medication(s) that may affect renal function, or result in significant haemodynamic change or may interfere with the disposition of metformin, such as cationic medicines that are eliminated by renal tubular secretion (see **section 4.5**), should be used with caution.
Radiologic studies involving the use of intravascular iodinated contrast materials (e.g. intravenous urogram, intravenous cholangiography, angiography and computed tomography (CT) scans with intravascular contrast materials): Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function, and have been reported to be associated with lactic acidosis in patients receiving metformin (see **section 4.5**). Therefore, in patients in whom any such study is planned, combination of sitagliptin and metformin should be temporarily discontinued at the time

of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

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

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

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

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

Vitamin B12 levels: In reported controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B12 levels, without clinical manifestations has been reported in approximately 7 % of patients. Such decrease possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is however, very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B12 supplementation. Measurement of haematologic parameters on an annual basis is advised in patients on sitagliptin/metformin combination and any apparent abnormalities should be appropriately investigated and managed.

Certain individuals (those with inadequate Vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B12 levels. In these patients, routine serum Vitamin B12 measurements at 2 to 3 year intervals may be useful.

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

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

Paediatric use

Safety and effectiveness of the combination of sitagliptin and metformin in paediatric patients under 18 years have not been reported.

Use in the elderly

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

Sitagliptin

The safety and effectiveness of sitagliptin in the elderly (65 years or older) have been reported to be comparable to those seen in younger patients (65 years or younger).

Metformin hydrochloride

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

Metformin is known to be substantially excreted by the kidneys and because the risk of serious adverse reactions to the medicine is greater in patients with impaired renal function, metformin should only be used in patients with normal renal function (see **section 4.3**).

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic medicine interaction with the combination of sitagliptin and metformin have not been reported; however such interactions have been reported with the individual components of **SITAGLIPTIN/METFORMIN 50/50; 50/850; 50/1000 SUN PHARMA**, sitagliptin and metformin.

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

Concomitant use not recommended

Alcohol

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

Iodinated contrast medicines

Sitagliptin/metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

Combinations requiring precautions for use

Some medicinal products can adversely affect renal function, which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.
Concomitant use of medicines that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use. Close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when such products are coadministered.

Glucocorticoids (given by systemic and local routes) beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment with such medicinal products. If

necessary, the dose of the anti-hyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

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

Sitagliptin

Sitagliptin did not have clinically meaningful effects on the pharmacokinetics of the following: Metformin, rosiglitazone, glyburide, simvastatin, warfarin and oral contraceptives. Sitagliptin has not been reported to inhibit CYP isoenzymes CYP3A4, 2C8 or 2C9. Sitagliptin is also not expected to inhibit CYP2D6, 1A2, 2C19 or 2B6 or to induce CYP3A4.

It has been reported that, concomitant medications that are commonly administered to patients with type 2 diabetes including cholesterol-lowering ~~a~~ medicines (e.g. statins, fibrates, ezetimibe), anti-platelet medicines (e.g. clopidogrel), antihypertensives (e.g. ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, hydrochlorothiazide), analgesics and non- steroidal anti-inflammatory medicines (e.g. naproxen, diclofenac, celecoxib), anti-depressants (e.g. bupropion, fluoxetine, sertraline), antihistamines (e.g. cetirizine), proton-pump inhibitors (e.g. omeprazole, lansoprozole), and medications for erectile dysfunction (e.g. sildenafil), did not have a clinically meaningful effect on sitagliptin pharmacokinetics.

There was a slight increase in the area under the curve (AUC 11 %) and mean peak medicine concentration (C_{max} 18 %) of digoxin with the co-administration 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 reported to be increased approximately 29 % and 68 % respectively, in subjects with co-administration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of ciclosporin, a potent probe inhibitor of p-glycoprotein. The reported changes in sitagliptin pharmacokinetics are not considered to be clinically meaningful.

Metformin hydrochloride

Glyburide: Co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics in type 2 diabetes patients. Decreases in glyburide AUC and C_{max} have been reported, but were highly variable. The clinical significance of this interaction has been reported to be uncertain.

Furosemide: Pharmacokinetic parameters of metformin-furosemide has been reported to be affected by co-administration in healthy subjects. 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 have been reported to be 31 % and 12 % smaller respectively, than when administered alone, and the terminal half-life has been reported to be decreased by 32 %, without any significant change in furosemide renal clearance. No information has been reported about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine: Co-administration of nifedipine has been reported to increase plasma metformin C_{max} and AUC by 20 % and 9 % respectively, and increased the amount excreted in the urine in normal healthy volunteers. T_{max} and half-life have been reported to be unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic medicines: Cationic medicines (e.g. amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim or vancomycin) that are eliminated by renal tubular secretion, theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine, has been reported in normal healthy volunteers. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of sitagliptin/metformin and/or the interfering medicine is recommended in patients who are taking cationic medications, that are excreted via the proximal renal tubular secretory system.

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

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

Metformin is negligibly bound to plasma proteins and is therefore, less likely to interact with highly protein-bound medicines such as salicylates, sulphonamides, chloramphenicol and probenecid, as compared to the sulphonylureas, which are extensively bound to serum proteins.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled reported studies in pregnant women with the combination of sitagliptin and metformin; therefore, the safety of the combination of sitagliptin and metformin in pregnant women is not known. Sitagliptin/metformin is not recommended for use in pregnancy.

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

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

Lactation

No studies in lactating animals have been reported with the combination of sitagliptin and metformin. Combination of sitagliptin and metformin should not be used by a woman who is breastfeeding an infant.

In studies reported with the individual active substances, both sitagliptin and metformin are excreted in the milk of lactating rats. Metformin is excreted in human milk in small amounts. It is not known whether sitagliptin is excreted in human milk. Sitagliptin/metformin must therefore not be used in women who are breast-feeding.

Fertility

Reported 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

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

Although, 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 sitagliptin/metformin is used in combination with a sulphonylurea or with insulin.

4.8 Undesirable Effects

Table
The adverse reaction reported in patients receiving sitagliptin in combination with metformin

	Sitagliptin with Metformin		**Sitagliptin with Metformin and a Sulphonylurea**	
System organ class	**Frequent**	**Less frequent**	**Frequent**	**Less frequent**
Investigations		Decreased blood glucose levels		
Nervous system disorders		Somnolence		
Gastrointestinal disorders	Nausea	Diarrhoea, Upper abdominal pain	Constipation	
Metabolism and nutrition disorders			Hypoglycaemia	

Table: The frequency of adverse reactions identified from reported placebo-controlled clinical studies of sitagliptin and metformin alone, and post-marketing experience

Adverse reaction	**Frequency of adverse reaction**

Blood and lymphatic system disorders	
thrombocytopenia	Less frequent
Immune system disorders	
hypersensitivity reactions including anaphylactic responses	Less frequent
Metabolism and nutrition disorders	
hypoglycaemia	frequent
Nervous system disorders	
somnolence	Less frequent
Respiratory, thoracic and mediastinal disorders	
interstitial lung disease	Less frequent
Gastrointestinal disorders	
diarrhoea	Less frequent
nausea	frequent
flatulence	frequent
constipation	Less frequent
upper abdominal pain	Less frequent
vomiting	frequent
acute pancreatitis	Less frequent
fatal and non-fatal haemorrhagic and necrotizing pancreatitis	Less frequent
Skin and subcutaneous tissue disorders	

pruritus	Less frequent
angioedema	Less frequent
rash	Less frequent
urticaria	Less frequent
cutaneous vasculitis	Less frequent
exfoliative skin conditions including Stevens-Johnson syndrome	Less frequent
bullous pemphigoid	Less frequent
Musculoskeletal and connective tissue disorders	
arthralgia	Less frequent
myalgia	Less frequent
pain in extremity	Less frequent
back pain	Less frequent
arthropathy	Less frequent
Renal and urinary disorders	
impaired renal function	Less frequent
acute renal failure	Less frequent

Additional information on the individual active substances of the fixed dose combination

Sitagliptin

In addition, in reported monotherapy studies of up to 24 weeks in duration of sitagliptin 100 mg once daily alone compared to placebo, adverse reactions considered as medicine-related

reported in patients treated with sitagliptin in excess (> 0,2 % and difference > 1 patient) of that in patients receiving placebo are headache, hypoglycaemia, constipation and dizziness.

In addition to the medicine-related adverse reactions described above, adverse events (reported regardless of causal relationship to medicinal product) occurring in at least 5 % and more commonly in patients treated with sitagliptin, included upper respiratory tract infection and nasopharyngitis. Additional adverse events that reported more frequently in patients treated with sitagliptin (not reaching the 5 % level, but occurring with an incidence of greater than 0.5 % higher with sitagliptin than that in the control group), included osteoarthritis and pain in extremity.

Post-marketing data

During post-marketing experience of the Combination of sitagliptin and metformin , the following additional adverse reactions have been reported frequency unknown : Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome (see **Section 4.4**); acute pancreatitis, including fatal and non-fatal haemorrhagic and necrotising pancreatitis (see **Section 4.4**); worsening renal function, including acute renal failure (sometimes requiring dialysis); upper respiratory tract infection; nasopharyngitis; constipation, vomiting; headache.

Metformin

Reported adverse reactions with metformin

The following side effects may occur with Metformin.

Adverse reaction	Frequency of adverse reaction
Metabolism and nutrition disorders	Less frequent: Decrease of vitamin B12 and folic acid absorption with decrease of serum levels during long-term use of metformin. This change is generally without clinical significance.
	Less frequent: Lactic acidosis (see **Section 4.4**).
Nervous system disorders	Frequent: Metallic taste.
Gastrointestinal disorders	Frequent: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These side effects occur most frequently during initiation of therapy and resolve spontaneously in most cases.
Skin and subcutaneous tissue disorders	Less frequent: Mild erythema in some hypersensitive individuals.

Laboratory test findings

Sitagliptin

The incidence of laboratory adverse experiences has been reported to be similar in patients treated with sitagliptin and metformin compared to patients treated with placebo and metformin. Across the reported clinical studies, a small increase in white blood cell count (approximately 200 cells/microlitre in WBC vs. placebo; mean baseline WBC approximately 6 600 cells/microlitre) has been reported due to a small increase in neutrophils. This observation has

been reported in most but not all studies. This change in laboratory parameters is not considered to be clinically relevant.

Metformin hydrochloride

In reported controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B12 levels without clinical manifestations, has been reported in approximately 7 % of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is however, very rarely reported with anaemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B12 supplementation (see **Section 4.4**).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Sitagliptin

Single doses of up to 800 mg sitagliptin has been reported to be generally well tolerated. Minimal increases in QTc, not considered to be clinically relevant, has been reported at a dose of 800 mg sitagliptin (see **section 5**). There is no reported data with doses above 800 mg in humans. In

reported Phase I multiple-dose studies, there were no dose-related clinical adverse reactions reported with sitagliptin with doses of up to 600 mg per day for 10 days and 400 mg per day for periods of up to 28 days.

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

Sitagliptin is modestly dialysable. Approximately 13.5 % of the dose has been reported to be removed over a 3 to 4 hour haemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.

Metformin hydrochloride

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

PHARMACOLOGICAL CLASSIFICATION:

A.21.2 Oral Hypoglycaemics

PHARMACOLOGICAL ACTION

Mechanism of Action

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

Sitagliptin

Sitagliptin is an orally-active, potent and 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 medicines 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.

Metformin hydrochloride

Metformin is an antihyperglycaemic medicines which lowers both basal and postprandial plasma glucose. Its pharmacologic mechanism of action are different from other classes of oral antihyperglycaemic medicines. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilisation.

5.2 Pharmacokinetic properties

Absorption

Sitagliptin

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

Metformin hydrochloride

The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50 to 60 %. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1 500 mg, and 850 mg to 2 550 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 vs. time curve (AUC), and a 35 minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Sitagliptin

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

Metformin hydrochloride

The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride tablets 850 mg averaged 654 ± 358 litre. Metformin is negligibly bound to plasma proteins, in contrast to sulphonylureas 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 to 48 hours and are generally less than 1 mcg/ml. in reported controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/ml, even at maximum doses.

Biotransformation

Sitagliptin

Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79 % of sitagliptin is excreted unchanged in the urine. Following a [^{14}C] sitagliptin oral dose, approximately 16 % of the radioactivity has been reported to be excreted as metabolites of sitagliptin. Six metabolites have been reported at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies reported that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

Metformin hydrochloride

Intravenous single-dose studies in normal subjects reported that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been reported in humans) nor biliary excretion.

Elimination

Sitagliptin

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

Elimination of sitagliptin reported 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 reported. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However ciclosporin, a p-glycoprotein inhibitor did not reduce the renal clearance of sitagliptin.

Metformin hydrochloride

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 medicine 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.

Special Populations

Type 2 diabetes

Sitagliptin

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 insufficiency

Sitagliptin/metformin hydrochloride should not be used in patients with renal insufficiency (see **section 4.3)**

Sitagliptin

An approximately 2-fold increase in the plasma AUC of sitagliptin has been reported in patients with moderate renal insufficiency, and an approximately 4-fold increase has been reported in patients with severe renal insufficiency and in patients with ESRD on haemodialysis, as compared to normal healthy control subjects.

Metformin hydrochloride

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic insufficiency

Sitagliptin

In patients with moderate hepatic insufficiency (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. These differences are not considered to be clinically meaningful.

There is no reported clinical data in patients with severe hepatic insufficiency (Child-Pugh score > 9). However because sitagliptin is primarily renally eliminated, severe hepatic insufficiency is not expected to affect the pharmacokinetics of sitagliptin.

Metformin hydrochloride

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

Gender

Sitagliptin

Gender had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of reported 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 analysed according to gender. Similarly, in reported

controlled clinical studies in patients with type 2 diabetes, the antihyperglycaemic effect of metformin has been comparable in males and females.

Elderly

Sitagliptin

Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of reported 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 reported 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 is reported that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Treatment with sitagliptin and metformin combination tablets should not be initiated in patients 80 years of age or older, unless measurement of creatinine clearance demonstrates that renal function is not reduced (see **section 4.4**).

Paediatric

No studies have been reported in paediatric patients.

Body Mass Index (BMI)

Sitagliptin

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropyl cellulose, Anhydrous Calcium hydrogen phosphate, Crospovidone, Hydrogenated Castor Oil, Glycerol dibehenate, and Magnesium stearate.

Film coating

Opadry® Complete film coating system 20A540048 Pink,

Opadry® Complete film coating system 20A540053 Pink,

Opadry® Complete film coating system 20A565037 Brown,

Isopropyl Alcohol and Methylene Chloride

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Return all unused or expired medicines to your pharmacist for safe disposal.

Do not dispose of unused medicines in drains or sewerage systems (e.g. toilets).

6.5 Nature and contents of container

HDPE Bottle Pack:

The product can be supplied in pack sizes of 28's, 30's, 56's, 60's and 200's comprising of an HDPE bottle with silica gel desiccants and child resistant closure with induction seal liner.

6.6 Special precautions for disposal and other handling

Return all unused or expired medicines to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewerage systems (e.g. toilets).

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

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Stormill Ext.1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER(S)

SITAGLIPTIN/METFORMIN 50/500 SUN PHARMA - 57/21.2/0068.065

SITAGLIPTIN/METFORMIN 50/850 SUN PHARMA - 57/21.2/0069.066

SITAGLIPTIN/METFORMIN 50/1000 SUN PHARMA - 57/21.2/0070.067

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08 July 2025

10. DATE OF REVISION OF THE TEXT

08 July 2025