Professional Information for SALUMET

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

SALUMET 50/500 film-coated tablets

SALUMET 50/1 000 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SALUMET 50/500: Each film-coated tablet contains 50 mg sitagliptin (as sitagliptin phosphate anhydrous) and 500 mg metformin hydrochloride.

SALUMET 50/1 000: Each film-coated tablet contains 50 mg sitagliptin (as sitagliptin phosphate anhydrous) and 1 000 mg metformin hydrochloride.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

SALUMET 50/500: White to off-white, capsule shaped, biconvex, film-coated tablets, debossed with “663” on one side and plain on the other side.

SALUMET 50/1 000: Reddish brown coloured, capsule shaped, biconvex, film-coated tablets, debossed with “664” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SALUMET is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus, already being treated with sitagliptin and metformin given separately.

SALUMET 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

Posology

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

Dosing recommendations:

The starting dose of SALUMET should be based on the patient's current regimen. SALUMET should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal side effects associated with metformin. The following doses are available:

- 50 mg sitagliptin/500 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, SALUMET 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 SALUMET 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 sulphonylureas-induced hypoglycaemia (see sections 4.4 and 4.8).

No studies have been performed specifically examining the safety and efficacy of SALUMET, in patients previously treated with other oral antihyperglycaemic medicines and switched to SALUMET. 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:

SALUMET should not be used in patients with renal failure or renal dysfunction, e.g. serum creatinine levels > 133 µmol/L (males), > 124 µmol/L (females) or abnormal creatinine clearance (see section 4.3).

Elderly patients:

As SALUMET is excreted by the kidneys, it 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 elderly patients (see sections 4.4 and 4.8).

Hepatic impairment:

SALUMET should not be used in patients with hepatic impairment (see section 4.3).

Paediatric population:

SALUMET 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.

Method of administration

For oral use.

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

4.3 Contraindications

- Hypersensitivity to sitagliptin, metformin or to any of the excipients listed in section 6.1.
- A history of severe hypersensitivity reaction, such as anaphylaxis or angioedema to SALUMET or any other gliptins (DPP-4) (see section 4.4).
- Renal disease or renal dysfunction, e.g. as suggested by serum creatinine levels ≥ 133 µmol/L [males], ≥ 124 µmol/L [females], or abnormal creatinine clearance which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction and septicaemia.
- Acute conditions with the potential to alter renal function (such as dehydration, severe infection and shock).
- SALUMET should be temporarily discontinued in patients undergoing radiological studies involving intravascular administration of iodinated contrast media because the use of such products may result in acute alteration of renal function (see sections 4.4 and 4.5).
- Any type of acute metabolic acidosis (such as lactic acidosis and diabetic ketoacidosis).
- Diabetic pre-coma.
- Acute or chronic disease which may cause tissue hypoxia (such as cardiac or respiratory failure, recent myocardial infarction, and shock).
- Hepatic impairment.
- Acute alcohol intoxication, alcoholism.
- Breastfeeding.

4.4 Special warnings and precautions for use

Post-marketing reports of serious hypersensitivity reactions in patients treated with

sitagliptin, one of the components of SALUMET, have been reported. 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 some reports occurring after the first dose. If a hypersensitivity reaction is suspected, SALUMET should be discontinued immediately. Other potential causes for the event should be assessed, and alternative treatment for diabetes initiated (see sections 4.3 and 4.8).

General:

SALUMET should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis (see section 4.3).

Acute pancreatitis:

Use of sitagliptin in SALUMET has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of SALUMET (with or without supportive treatment), but cases of necrotising or haemorrhagic pancreatitis and/or death have been reported (see section 4.8). If pancreatitis is suspected, SALUMET and other potentially suspect medicines should be discontinued. If acute pancreatitis is confirmed, SALUMET should not be restarted.

Caution should be exercised in patients with a history of pancreatitis.

Lactic acidosis:

Lactic acidosis, a rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. The risk of lactic acidosis is increased by metformin accumulation during treatment with SALUMET (sitagliptin phosphate/metformin hydrochloride). When it occurs, it is fatal in approximately 50 % of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus and whenever there is significant tissue hypoperfusion and hypoxaemia. Lactic acidosis is

characterised by elevated blood lactate levels (> 5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels greater than 5 µg/mL are generally found.

In case of dehydration (severe vomiting, diarrhoea, fever or reduced fluid intake), metformin should temporarily be discontinued, and it is recommended that a health care provider is consulted.

Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion (see section 4.3), often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medicines. 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 (see section 4.3), 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 withheld in the presence of any condition associated with hypoxaemia, dehydration or sepsis (see section 4.3).

Medicines that can acutely impair renal function (such as antihypertensives, diuretics and nonsteroidal anti-inflammatory medicines [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 (see sections 4.3 and 4.5).

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

Patients and/or caregivers 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 SALUMET and seek immediate medical attention. 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. 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:

Metformin and sitagliptin are known to be excreted substantially 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 SALUMET. In patients with advanced age, SALUMET should be carefully titrated to establish the minimum dose for adequate glycaemic effect, because ageing 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 SALUMET 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 SALUMET discontinued if evidence of renal impairment is present.

Hypoglycaemia:

Patients receiving SALUMET in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a reduction in the dose of the sulphonylurea may be necessary.

Hypoglycaemia does not occur in patients receiving metformin alone under usual circumstances, but could occur when caloric intake is insufficient, 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. It may be difficult to recognise hypoglycaemia in elderly patients and in people who are taking ß-adrenergic blocking medicines.

Bullous pemphigoid:

There have been reports of bullous pemphigoid in patients taking DPP-4 inhibitors including sitagliptin. SALUMET should be discontinued if bullous pemphigoid is suspected.

Surgical procedures:

Use of SALUMET should be temporarily suspended at the time of 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 nutrition has resumed and renal function has been re-evaluated and found to be stable (see section 4.3).

Administration of iodinated contrast media:

Intravascular administration of iodinated contrast media may lead to contrast-induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. SALUMET should 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 (see sections 4.3 and 4.5).

Change in clinical status of patients with previously controlled type 2 diabetes:

If a patient with type 2 diabetes previously well controlled on SALUMET develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness), prompt evaluation for evidence of ketoacidosis or lactic acidosis is necessary. Serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels should form part of the evaluation. If either form of acidosis occurs, SALUMET must be stopped immediately, and other appropriate corrective measures initiated.

Hypoxic states:

Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction and other conditions characterised by hypoxaemia have been associated with lactic acidosis and may also cause pre-renal azotaemia. SALUMET therapy should be discontinued immediately when such events occur in patients on SALUMET treatment (see section 4.3).

Alcohol intake:

Since alcohol is known to potentiate the effect of metformin or lactate metabolism, patients should be warned against excessive alcohol intake, acute or chronic, while taking SALUMET (see section 4.3).

Impaired hepatic function:

Since impaired hepatic function has been associated with some cases of lactic acidosis, SALUMET is contraindicated in patients with clinical or laboratory evidence of hepatic disease (see section 4.3).

Vitamin B_{12} levels:

SALUMET can possibly interfere with vitamin B_{12} absorption from the B_{12}-intrinsic factor complex and cause a decrease in serum vitamin B_{12} levels from previously normal serum vitamin B_{12} levels to subnormal levels. It is, however, very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin in SALUMET or vitamin B_{12} supplementation. Haematological parameters should be measured on an annual basis in patients taking SALUMET and any apparent abnormalities should be investigated and managed appropriately. Caution is advised when administering SALUMET to certain individuals (with inadequate vitamin B_{12} or calcium intake or absorption) who appear to be predisposed to developing subnormal levels of vitamin B_{12}.

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, it may lead to a temporary loss of glycaemic control. It may be necessary to withhold SALUMET and temporarily administer insulin, during such times. SALUMET may be reinstituted after the acute episode is resolved.

4.5 Interaction with other medicines and other forms of interaction

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

Pharmacokinetic interaction studies with SALUMET have not been performed; however, such studies have been conducted with the individual active ingredients contained in SALUMET, i.e. sitagliptin and metformin.

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 (see section 4.3).

Iodinated contrast medicines: SALUMET 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 (see sections 4.3 and 4.4).

Combinations requiring precautions for use:
Some medicines can adversely affect renal function, which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclooxygenase II (COX-II) inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with SALUMET, 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. Close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when such products are co-administered.

Glucocorticoids (given by systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed, and more frequent blood glucose monitoring performed, especially at the beginning of treatment with such medicines. If necessary, the dose of SALUMET should be adjusted during therapy with the other medicines and on its discontinuation.

ACE inhibitors may decrease the blood glucose levels. If necessary, the dose of the SALUMET should be adjusted during therapy with the other medicines and on its discontinuation.

Effects of other medicines on sitagliptin:
In vitro and clinical data described below suggest that the risk for clinically meaningful interactions following coadministration of other medicines is low.

In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin is CYP3A4, with contribution from CYP2C8. In patients with normal renal function, metabolism, including via CYP3A4, plays only a small role in the clearance of sitagliptin. Metabolism may play a more significant role in the elimination of sitagliptin in the setting of severe renal impairment or end-stage renal disease (ESRD). For this reason, it is possible that potent CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the pharmacokinetics of sitagliptin in patients with severe renal impairment or ESRD. The effects of potent CYP3A4 inhibitors in the setting of renal impairment have not been assessed in a clinical study.

In vitro transport studies showed that sitagliptin is a substrate for p-glycoprotein and organic anion transporter-3 (OAT3). OAT3 mediated transport of sitagliptin was inhibited *in vitro* by probenecid, although the risk of clinically meaningful interactions is considered to be low. Concomitant administration of OAT3 inhibitors has not been evaluated *in vivo*.

Ciclosporin: A study was conducted to assess the effect of ciclosporin, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Co-administration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of ciclosporin increased the AUC and C_{max} of sitagliptin by approximately 29 % and 68 %, respectively. These changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

Effects of sitagliptin on other medicines:

Digoxin: Sitagliptin had a small effect on plasma digoxin concentrations. Following administration of 0,25 mg digoxin concomitantly with 100 mg of sitagliptin daily for 10 days, the plasma AUC of digoxin was increased on average by 11 %, and the plasma C_{max} on average by 18 %. No dose adjustment of digoxin is recommended. However, patients at risk of digoxin toxicity should be

monitored for this when sitagliptin and digoxin are administered concomitantly.

In vitro data suggest that sitagliptin does not inhibit nor induce CYP450 isoenzymes. In clinical studies, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing *in vivo* evidence of a low propensity for causing interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT). Sitagliptin may be a mild inhibitor of p-glycoprotein *in vivo*.

Population pharmacokinetic analyses have been conducted in patients with type 2 diabetes. Concomitant medicines did not have a clinically meaningful effect on sitagliptin pharmacokinetics. Medicines assessed were those that are commonly administered to patients with type 2 diabetes including cholesterol-lowering medicines (e.g. statins, fibrates, ezetimibe), antiplatelet medicines (e.g. clopidogrel), antihypertensives (e.g. ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, hydrochlorothiazide), analgesics and NSAIDs (e.g. naproxen, diclofenac, celecoxib), antidepressants (e.g. bupropion, fluoxetine, sertraline), antihistamines (e.g. cetirizine), proton pump inhibitors (e.g. omeprazole, lansoprazole), and medicines for erectile dysfunction (e.g. sildenafil).

Effect of metformin on other medicines:

Glyburide: In a single-dose interaction study in type 2 diabetes patients, co-administration 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 medicine interaction study in healthy volunteers demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. 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 co-administered chronically.

Nifedipine: A single-dose, metformin-nifedipine medicine interaction study in normal healthy volunteers demonstrated that co-administration 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.

Cationic medicines (e.g. amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim or vancomycin): Cationic medicines are eliminated by renal tubular secretion and 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 observed in normal healthy volunteers in both single- and multiple-dose metformin-cimetidine medicine interaction studies, with a 60 % increase in peak metformin plasma and whole blood concentrations, and a 40 % increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of SALUMET and/or the interfering medicine is recommended in patients who are taking cationic medicines, 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 SALUMET, the patient should be closely observed to maintain adequate

glycaemic control.

In healthy volunteers, the pharmacokinetic properties of metformin and propranolol, and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is therefore less likely to interact with highly protein bound 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 data from the use of sitagliptin in SALUMET in pregnant women. Studies have shown reproductive toxicity at high doses.

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

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

Breastfeeding

No studies in lactating animals have been conducted with the combined active substances of SALUMET. 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. SALUMET must therefore not be used in women who are breastfeeding (see section 4.3)

Fertility

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

4.7 Effects on ability to drive and use machines

When driving or using machines, it should be taken into account that dizziness and somnolence have been reported with sitagliptin in SALUMET and caution is advised until the effects of SALUMET are known.

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

4.8 Undesirable effects

Summary of the safety profile

There have been no therapeutic clinical trials conducted with SALUMET however, bioequivalence of SALUMET with co-administered sitagliptin and metformin has been demonstrated (see section 5.2). 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 %).

Table 1: The frequency of adverse reactions identified from 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, *#angioedema	frequency not known
Metabolism and nutrition disorders	
#hypoglycaemia	frequent
Nervous system disorders	
somnolence	less frequent
Respiratory, thoracic and mediastinal disorders	
*interstitial lung disease, *upper respiratory tract infection, *nasopharyngitis	frequency not known
Gastrointestinal disorders	
nausea, flatulence, vomiting	frequent
diarrhoea, constipation, upper abdominal pain	less frequent
*#acute pancreatitis, *#fatal and non-fatal haemorrhagic and necrotising pancreatitis	frequency not known
Skin and subcutaneous tissue disorders	
*pruritus	less frequent

*#rash, *#urticaria, *#cutaneous vasculitis, *#exfoliative skin conditions including Stevens-Johnson syndrome, *bullous pemphigoid	frequency not known
Musculoskeletal and connective tissue disorders	
*arthralgia, *myalgia, *back pain, *arthropathy	frequency not known
Renal and urinary disorders	
*impaired renal function, *acute renal failure	frequency not known

* Adverse reactions were identified post-marketing.

See section 4.4.

Description of selected adverse reactions

Some adverse reactions were observed more frequently in studies of combination use of sitagliptin and metformin in SALUMET with other antidiabetic medicines than in studies of sitagliptin and metformin alone. These included hypoglycaemia (occurring frequently with sulphonylurea or insulin), constipation (occurring frequently with sulphonylurea), peripheral oedema (occurring frequently with pioglitazone or the combination of pioglitazone), and headache and dry mouth (occurring less frequently 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 (> 0,5 % higher among sitagliptin users than that in the control group).

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 (frequent), lactic acidosis, liver function disorders, hepatitis, urticaria, erythema, and pruritus (less frequent). Long-term treatment with metformin has been associated with a decrease in vitamin B_{12} absorption which may very rarely result in clinically significant vitamin B_{12} deficiency (e.g. megaloblastic anaemia).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of SALUMET is important. It allows continued monitoring of the benefit/risk balance of SALUMET. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:
https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

During controlled clinical trials 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.

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. 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.

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. Lactic acidosis has been reported in approximately 32 % of metformin overdose cases. Metformin is dialysable with a clearance of up to 170 mL/min under good haemodynamic conditions. Therefore, haemodialysis is the most effective method to remove lactate and metformin.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.2 Oral hypoglycaemics.
Pharmacotherapeutic group: Drugs used in diabetes, Combinations of oral blood glucose lowering drugs.
ATC code: A10BD07.

SALUMET combines two antihyperglycaemic medicines 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 is 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 physiological 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 (PPARγ) agonists, alpha glucosidase inhibitors, and amylin analogues.

Sitagliptin administered on its own increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Co-administration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations.

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 utilisation.
- 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

A bioequivalence study in healthy subjects demonstrated that a combination tablet containing sitagliptin and metformin is 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 SALUMET.

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 micromolar hours, C_{max} was 950 nM. The absolute bioavailability of sitagliptin is approximately 87 %. Since co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, SALUMET 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_{24h} (C_{max} increased in a greater than dose-proportional manner and C_{24h} 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 litres. 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 isozymes 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, ciclosporin, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin. Sitagliptin is not a substrate for OCT2 or OAT1 or $PEPT_{1/2}$ transporters. *In vitro*, sitagliptin did not inhibit OAT3 (IC50 = 160 µM) or p-glycoprotein (up to 250 µM) mediated transport at therapeutically relevant plasma concentrations. In a clinical study sitagliptin had a small effect on plasma digoxin concentrations indicating that sitagliptin may be a mild inhibitor of p-glycoprotein.

Metformin

Absorption:

After an oral dose of metformin, T_{max} is reached in 2,5 hours. 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 hours and are generally less than 1 µg/mL. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 5 µg/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-minute 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 V_d ranged between 63 L and 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 hours. 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.

Special populations

Type 2 diabetes:

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

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

Renal insufficiency:

SALUMET 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 was observed in patients with moderate renal insufficiency, and an approximately 4-fold increase was observed in patients with severe renal insufficiency and in patients with ESRD on haemodialysis, as compared to normal healthy control subjects.

Metformin: 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 impairment:

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 phosphate. These differences are not considered to be clinically meaningful.

There is no clinical experience 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: No pharmacokinetic studies of metformin have been conducted in patients with hepatic insufficiency.

Gender:

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

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

Elderly patients:

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

to younger subjects.

Metformin: Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with ageing is primarily accounted for by a change in renal function.

Treatment with SALUMET 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 patients:

No studies have been performed in paediatric patients.

Body mass index (BMI):

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose (E460)

Croscarmellose sodium (E468)

Povidone

Hydroxypropyl cellulose

Sodium stearyl fumarate

Magnesium stearate (E572).

Film-coating:

SALUMET 50/500

Opadry II White consisting of:

Polyvinyl alcohol (E1203)

Titanium dioxide (E171)

Macrogol (E1521)

Talc (E553b).

SALUMET 50/1 000

Opadry II Brown consisting of:

Polyvinyl alcohol (E1203)

Macrogol (E1521)

Titanium dioxide (E171)

Talc (E553B)

Iron oxide yellow (E172)

Iron oxide red (E172)

FD&C No. 6 Yellow/Sunset Yellow (E110).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister strips in the outer carton and keep the bottle well closed until required for use.

6.5 Nature and contents of container

OPA/Alu/PVC/Alu blister strips containing 10 tablets each packed in an outer carton.

Or

White HDPE screw neck bottle with a white polypropylene child-resistant screw cap with liner.

Pack size: 30 or 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building B, Ground Floor

22 Karee Street

Centurion, Pretoria

0157

8. REGISTRATION NUMBERS

SALUMET 50/500: 52/21.2/0913

SALUMET 50/1 000: 52/21.2/0914

9. DATE OF FIRST AUTHORISATION

07 December 2021

10. DATE OF REVISION OF THE TEXT

Not applicable.