PROFESSIONAL INFORMATION

SCHEDULING STATUS S3

1 NAME OF THE MEDICINE

GLUSITA PLUS 50 mg/500 mg (film-coated tablets)

GLUSITA PLUS 50 mg/850 mg (film-coated tablets)

GLUSITA PLUS 50 mg/1 000 mg (film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each GLUSITA PLUS 50 mg/500 mg (film-coated tablet) contains sitagliptin phosphate monohydrate equivalent to 50 mg sitagliptin and 500 mg metformin hydrochloride.

Each GLUSITA PLUS 50 mg/850 mg (film-coated tablet) contains sitagliptin phosphate monohydrate equivalent to 50 mg sitagliptin and 850 mg metformin hydrochloride.

Each GLUSITA PLUS 50 mg/1 000 mg (film-coated tablet) contains sitagliptin phosphate monohydrate equivalent to 50 mg sitagliptin and 1 000 mg metformin hydrochloride.

GLUSITA PLUS is sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

GLUSITA PLUS 50 mg/500 mg (film-coated tablet).

Pink oval biconvex film-coated tablet debossed with “SM01” on one side.

GLUSITA PLUS 50 mg/850 mg (film-coated tablet).

Light orange oval biconvex film-coated tablet debossed with “SM02” on one side.

GLUSITA PLUS 50 mg/1 000 mg (film-coated tablet).

Light red oval biconvex film-coated tablet debossed with “SM03” on one side.

4 CLINICAL PARTICULARS

4.1. Therapeutic indications

GLUSITA PLUS 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.

GLUSITA PLUS is also indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control 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 GLUSITA PLUS 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.

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

Posology:

Dosing Recommendations:

The starting dose of GLUSITA PLUS should be based on the patient's current regimen. GLUSITA PLUS 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, GLUSITA PLUS 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 GLUSITA PLUS 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 sections 4.4 and 4.8).

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

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

Elderly:

As metformin and sitagliptin are excreted by the kidneys, GLUSITA PLUS should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly (see section 4.4, "Lactic acidosis").

Paediatric Population:

GLUSITA PLUS 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.

4.3 Contraindications

GLUSITA PLUS (sitagliptin phosphate monohydrate / metformin hydrochloride) is contraindicated in patients with:

1. Known hypersensitivity (including a history of severe hypersensitivity reaction, such as anaphylaxis or angioedema) to sitagliptin phosphate monohydrate, metformin hydrochloride or any other component of GLUSITA PLUS listed in section 6.1 or any other gliptins (DPP-4).
2. 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.
3. Acute or chronic metabolic acidosis (lactic acidosis, diabetic ketoacidosis, with or without coma).
4. Diabetic pre-coma.
5. Acute conditions with the potential to alter renal function such as:
   - dehydration
   - severe infection
   - shock
6. Acute or chronic disease which may cause tissue hypoxia such as:
   - cardiac or respiratory failure
   - recent myocardial infarction
   - shock
7. Hepatic impairment.
8. Acute alcohol intoxication, alcoholism.
9. Breast-feeding.

GLUSITA PLUS should be temporarily discontinued and not restarted until at least 48 hours after the procedure 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

sections 4.4.and 4.8).

4.4 Special warnings and precautions for use

General:

GLUSITA PLUS should not be used in patients with type 1 diabetes and must not be used for the treatment of diabetic ketoacidosis.

Acute pancreatitis:

Use of DPP-4 inhibitors 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 sitagliptin (with or without supportive treatment), but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, GLUSITA PLUS and other potentially suspect medicines should be discontinued; if acute pancreatitis is confirmed, GLUSITA PLUS 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. 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. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

Diagnostic laboratory findings are decreased blood pH (< 7,35), increased plasma lactate levels (> 5 mmol/L), 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.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low

(approximately 0,03 cases/1000 patient-years, with approximately 0,015 fatal cases/1000 patient-years). In more than 20 000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. 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 withheld in the presence of any condition associated with hypoxaemia, dehydration or sepsis. In case of dehydration (severe vomiting, diarrhoea, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

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.

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

cause lactic acidosis (see sections 4.3 and 4.5).

Patients and/or caregivers should be informed of the risk of lactic acidosis. The onset of lactic acidosis often is subtle, and accompanied only by non-specific symptoms. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia, malaise, increasing somnolence and hypothermia followed by coma. There may be associated hypotension and resistant bradyarrhythmias with more marked acidosis. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention.

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/L in patients taking metformin, do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity or technical problems in sample handling.

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

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

Renal function:

GFR should be assessed before treatment initiation and regularly thereafter (see section 4.2). GLUSITA PLUS is contraindicated in patients with GFR < 30 ml/min and should be temporarily discontinued during conditions with the potential to alter renal function.

Hypoglycaemia:

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

Hypersensitivity reactions:

Post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin 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 sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, GLUSITA PLUS should be discontinued, other potential causes of the event should be assessed, and alternative treatment for diabetes should be instituted (see section 4.8).

Bullous pemphigoid:

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

Surgery:

GLUSITA PLUS 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.

Administration of iodinated contrast materials:

Intravascular administration of iodinated contrast materials may lead to contrast-induced nephropathy,

resulting in metformin accumulation and an increased risk of lactic acidosis. GLUSITA PLUS 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:

A patient with type 2 diabetes mellitus previously well controlled on GLUSITA PLUS 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, treatment must be stopped immediately, and other appropriate corrective measures initiated.

Hypoxic states:

Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterised by hypoxaemia have been associated with lactic acidosis and may also cause pre-renal azotaemla. When such events occur in patients on GLUSITA PLUS therapy, GLUSITA PLUS should be promptly discontinued.

Alcohol Intake:

Alcohol ls known to potentiate the effect of metformin on lactate metabolism. Patients should therefore, be warned against excessive alcohol intake, acute or chronic, while receiving GLUSITA PLUS.

Impaired hepatic function:

Since impaired hepatic function has been associated with some cases of lactic acidosis, GLUSITA PLUS should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} levels:

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of

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

Certain individuals (those with inadequate Vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B_{12} levels. In these patients, routine serum Vitamin B_{12} measurements at 2 to 3 year intervals may be useful.

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 GLUSITA PLUS and temporarily administer insulin. GLUSITA PLUS may be reinstituted after the acute episode is resolved.

Use in the elderly:

Because sitagliptin and metformin are substantially excreted by the kidney and because aging can be associated with reduced renal function, GLUSITA PLUS 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.

In clinical studies, the safety and effectiveness of sitagliptin in the elderly (65 years or older were comparable to those seen in younger patients (65 years or younger).

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).

Laboratory test findings:

The incidence of laboratory adverse experiences was similar in patients treated with sitagliptin and metformin compared to patients treated with placebo and metformin. Across clinical studies, a small Increase in white blood cell count (approximately 200 cells/microlitre in WBG vs. placebo; mean baseline WBC approximately 6 600 cells/microlitre) was observed due to a small increase in neutrophils. This observation was seen in most but not all studies. This change in laboratory parameters is not considered to be clinically relevant

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels without clinical manifestations, was observed in approximately 7 % of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is however, very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation.

Sodium:

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

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 mellitus.

Pharmacokinetic medicine interaction studies with GLUSITA PLUS have not been performed; however, such studies have been conducted with the individual active substances, 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.

Iodinated contrast materials:

GLUSITA PLUS 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 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 medicines 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 the anti-hyperglycaemic medicines should be adjusted during therapy with the other medicine and on its discontinuation.

ACE-inhibitors may decrease the blood glucose levels. If necessary, the dose of the anti-hyperglycaemic medicine should be adjusted during therapy with the other medicine 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 co-administration 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*.

Metformin hydrochloride:

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 subjects 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:

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 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 % 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 GLUSITA PLUS 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 GLUSITA PLUS,

the patient should be closely observed to maintain adequate glycaemic control.

In healthy volunteers the pharmacokinetics 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 pregnant women. Studies in animals have shown reproductive toxicity at high doses of sitagliptin.

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

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

Breast-feeding:

No studies in lactating animals have been conducted with the combined active substances of this medicine. 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. GLUSITA PLUS must therefore not be used in women who are breast-feeding (see section 4.3).

Fertility:

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

data are lacking.

4.7. Effects on ability to drive and use machines

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

In addition, patients should be alerted to the risk of hypoglycaemia when GLUSITA PLUS 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 GLUSITA PLUS tablets however bioequivalence of GLUSITA PLUS 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 %).

Sitagliptin and metformin:

Adverse reactions are listed below as MedDRA preferred term by system organ class and absolute frequency (Table 1).

Table 1: The frequency of adverse reactions identified from placebo-controlled clinical studies of sitagliptin and metformin alone, and post-marketing experience

System Organ Class	**Frequent**	**Less frequent**	**Frequency Unknown**
Blood and Lymphatic System		Thrombocytopenia	

Disorders			
Immune System Disorders			Hypersensitivity reactions including anaphylactic responses*,†
Metabolism and Nutrition Disorders	Hypoglycaemia†		
Nervous System Disorders	Metallic taste	Somnolence	
Respiratory, Thoracic and Mediastinal Disorders		Lactic acidosis, Decrease of vitamin B_{12} and folic acid absorption with decrease of serum levels during long-term use of metformin. This change is generally without clinical significance	Interstitial lung disease*
Gastrointestinal Disorders	Nausea, Flatulence, Vomiting Loss of appetite	Diarrhoea, Constipation, Upper abdominal pain	Acute pancreatitis*,†,‡ Fatal and non-fatal haemorrhagic and necrotising pancreatitis*,†

Skin and Subcutaneous Tissue Disorders		Pruritus, Mild erythema in some hypersensitive individuals	Angioedema*,† Rash*,† Urticaria*,† Cutaneous vasculitis*,† Exfoliative skin conditions including Stevens-Johnson syndrome*,† Bullous pemphigoid*
Musculoskeletal and connective tissue disorders			Arthralgia* Myalgia* Pain in extremity* Back pain* Arthropathy*
Renal and Urinary Disorders			Impaired renal function* Acute renal failure*
Investigations		Decreased blood glucose levels	

*Adverse reactions were identified through post-marketing surveillance.

† See section 4.4.

‡ See *TECOS Cardiovascular Safety Study* below.

Description of selected adverse reactions:

Some adverse reactions were observed more frequently in studies of combination use of sitagliptin and

metformin with other anti-diabetic medicines than in studies of sitagliptin and metformin alone. These included hypoglycaemia (frequent with sulphonylurea or insulin), constipation (frequent with sulphonylurea), peripheral oedema (frequent with pioglitazone), and headache and dry mouth (less frequent 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 medicine occurring in at least 5 % included upper respiratory tract infection and nasopharyngitis. In addition, osteoarthritis and pain in extremities were reported less frequently (> 0.5 % higher among sitagliptin users than that in the control group).

Metformin:

Gastrointestinal symptoms were reported frequently 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).

TECOS Cardiovascular Safety Study:

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7,332 patients treated with sitagliptin, 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and < 50 ml/min/1,73 m^2), and 7 339 patients treated with placebo in the intention-to-treat population. Both treatments were added to usual care targeting regional standards for HbA1c and CV risk factors. The overall incidence of serious adverse events in patients receiving sitagliptin was similar to that in patients receiving placebo.

In the intention-to-treat population, among patients who were using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycaemia was 2,7 % in sitagliptin-treated patients and 2,5 % in placebo-treated patients; among patients who were not using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycaemia was 1,0 % in sitagliptin-treated patients and 0,7 % in placebo-treated patients. The incidence of adjudication-confirmed pancreatitis events was 0,3 % in sitagliptin-treated patients and 0,2 % in placebo-treated patients.

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. 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.
Suspected adverse reactions can also be reported directly to the HCR via Patientsafety.sacg@novartis.com.

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.

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

In clinical studies, approximately 13,5 % of the dose was removed over a 3 to 4 hour haemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin

is dialysable by peritoneal dialysis.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and class: A21.2 Oral hypoglycaemics.

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

GLUSITA PLUS 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 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. 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, alphaglucosidase inhibitors, and amylin analogues.

In a two-day study in healthy subjects, sitagliptin alone 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).

Paediatric population:

See section 4.2 for information on paediatric use.

5.2. Pharmacokinetic properties

Absorption:

Sitagliptin:

Following oral administration of a 100 mg dose to healthy subjects, sitagliptin was absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8,52 µm•hr, 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, sitagliptin may be administered with or without food.

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

Metformin:

After an oral dose of metformin, T_{max} is reached in 2,5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50 - 60 % in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20 - 30 %.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 - 48 h and are generally less than 1 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 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease 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:

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

Biotransformation:

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 was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

In vitro data showed that sitagliptin is not an inhibitor of CYP isoenzymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4 and CYP1A2.

Metformin:

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

Elimination:

Sitagliptin:

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 PEPT1/2 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:

Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6,5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

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 impairment:

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

Sitagliptin:

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

Compared to normal healthy control subjects, plasma AUC of sitagliptin was increased by approximately 1,2 fold and 1,6 fold in patients with mild renal impairment (GFR ≥ 60 to < 90 ml/min) and patients with moderate renal impairment (GFR ≥ 45 to < 60 ml/min), respectively. Because increases of this magnitude are not clinically relevant, dosage adjustment in these patients is not necessary.

Plasma AUC of sitagliptin was increased approximately 2 fold in patients with moderate renal impairment (GFR ≥ 30 to < 45 ml/min), and approximately 4 fold in patients with severe renal impairment (GFR < 30 ml/min), including patients with ESRD on haemodialysis. Sitagliptin was modestly removed by haemodialysis (13,5 % over a 3 to 4 hour haemodialysis session starting 4 hours post-dose).

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:

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

Metformin:

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

Gender:

Sitagliptin:

No dose adjustment is necessary based on gender. This characteristic 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:

Sitagliptin:

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

Metformin:

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

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 sections 4.4.and 4.8).

Paediatric:

No studies with sitagliptin have been performed in paediatric patients.

Body Mass Index (BMI):

Sitagliptin:

No dose adjustment is necessary based on body mass index (BMI). This characteristic 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:

Povidone K30

Sodium lauryl sulfate

Microcrystalline cellulose

Croscarmellose sodium

Sodium stearyl fumarate

Film-coating:

HPMC (Hypromellose type 2910)

Hydroxypropyl cellulose

Triethyl citrate

Titanium dioxide, E172

Talc

Ferric oxide, red, E171

Ferric oxide, yellow, E171 (50 mg/850 mg & 50 mg/1000 mg strengths only).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store below 30 °C

6.5. Nature and contents of container

GLUSITA PLUS film-coated tablets are packed in Al / Al blisters and PVDC blisters, in packs of 28 and 56 tablets with blisters of 7 tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Waterfall 5-Ir

Magwa Crescent West

Waterfall City

Jukskei View

2090

8. REGISTRATION NUMBERS

GLUSITA PLUS 50 mg/500 mg: 55/21.2/0676

GLUSITA PLUS 50 mg/850 mg: 55/21.2/0677

GLUSITA PLUS 50 mg/1 000 mg: 55/21.2/0678

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 February 2023.

10. DATE OF REVISION OF THE TEXT

Not applicable.

[1]Company Reg. No.: 1990/001979/07