PI for METSITAG 50 mg/500 mg and 50 mg/1000 mg

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

METSITAG 50 mg/500 mg film-coated tablets.

METSITAG 50 mg/1000 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

METSITAG 50 mg/500 mg: Each tablet contains sitagliptin phosphate monohydrate equivalent to 50 mg of sitagliptin and 500 mg metformin hydrochloride.

METSITAG 50 mg/1000 mg: Each tablet contains sitagliptin phosphate monohydrate equivalent to 50 mg of sitagliptin and 1000 mg metformin hydrochloride.

METSITAG is sugar free.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablets

METSITAG 50 mg/500 mg:

Light pink colour capsule shape, biconvex film coated tablets, debossed with “C 77” on one side and plain on the other side.

METSITAG 50 mg/1000 mg:

Red colour capsule shape, biconvex, film coated tablets, debossed with “C 78” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

METSITAG 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.

METSITAG 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 agents: Metformin, sitagliptin or a sulphonylurea.

4.2 Posology and method of administration

Posology

The dosage of antihyperglycemic therapy with **METSITAG** 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.

Dosing recommendations:

The starting dose of **METSITAG** should be based on the patient's current regimen. **METSITAG** should be given twice daily with meals. The following doses are available:

Sitagliptin 50 mg and metformin hydrochloride 500 mg

Sitagliptin 50 mg and metformin hydrochloride 1000 mg

For patients switching from co-administration of sitagliptin and metformin

For patients switching from co-administration of sitagliptin and metformin, **METSITAG** 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 agents: Sitagliptin, metformin or a sulphonylurea.

The usual starting dose of **METSITAG** should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose). In determining the starting dose of the metformin component, the patient's level of glycaemic control and current dose of metformin should be considered. Gradual dose escalation to reduce the gastrointestinal (GI) side effects associated with metformin should be considered. Patients currently on or initiating a sulphonylurea may require lower sulphonylurea doses to reduce the risk of sulphonylurea-induced hypoglycaemia (see section 4.4 and 4.8).

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

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

Elderly

As sitagliptin and metformin are excreted by kidneys, **METSITAG** 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 4.8 section 4.4).

Paediatric population:

METSITAG 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

METSITAG 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

METSITAG is contraindicated in patients with:

1. Known hypersensitivity to sitagliptin phosphate, metformin hydrochloride or any other excipients listed in section 6.1 (see sections 4.4 and 4.8).

2. Renal disease or renal dysfunction e.g. as suggested by serum creatinine levels ≥ 133 micromol/ [males], ≥124 micromol/l [females], or abnormal creatine clearance which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction and septicaemia.

3. Acute or chronic metabolic acidosis including diabetic ketoacidosis with or without coma.

METSITAG should be discontinued temporarily in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, since the use of such products may result in acute alteration of renal function (see sections 4.4 and 4.8).

A history of severe hypersensitivity reaction, such as anaphylaxis or angioedema to **METSITAG** or any other gliptins (DPP-4).

4.4 Special warnings and precautions for use

General

METSITAG should not be given to patients with type 1 diabetes and must not be used for the treatment of diabetic ketoacidosis.

Pancreatitis:

There have been reports of acute pancreatitis in post-marketing experience including fatal and non-fatal haemorrhagic or necrotizing pancreatitis (see section 4.8), in patients taking sitagliptin. Patients must be informed of the characteristic symptom of acute pancreatitis: Persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of sitagliptin. If pancreatitis is suspected, **METSITAG** and other potentially suspect medicines should be discontinued immediately. If acute pancreatitis is confirmed, **METSITAG** should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Hypersensitivity reactions: In the post-marketing experience, there have been reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the ingredients of **METSITAG.** These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, **discontinue METSITAG** immediately, and institute an alternative class of medicines for treatment for diabetes (see section 4.3 and 4.8).

Lactic acidosis: Lactic acidosis is a serious (high mortality in the absence of prompt treatment), metabolic complication that most often occurs at acute worsening of renal function and increases the risk of lactic acidosis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

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.

Medicines that can acutely impair function (such as antihypertensives, diuretics and NSAIDS) should be initiated with caution in metformin-treated patients.

The risk of lactic acidosis may be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any conditions associated with hypoxia as well as concomitant use of medicines that may cause lactic acidosis (see section 4.5)

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7,35), increased plasma lactate levels (> 5mmol/L) and an increased anion gap and lactate/pyruvate ratio.

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)

Use in the elderly

As sitagliptin and metformin are excreted by kidneys, **METSITAG** 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 and 4.8).

Monitoring of renal function

Sitagliptin and metformin are known to be excreted by kidney substantially. The risk of accumulated metformin, and lactic acidosis increases with degree of impairment of renal function. Thus, patients with serum creatinine levels above upper limit of normal for age should not receive **METSITAG**. In advanced age patients, **METSITAG** should carefully be titrated to establish minimum dose for adequate glycaemic effect, because aging can be associated with reduced renal function. In elderly patients, mainly those 80 years of age and older, renal function should be monitored frequently.

Before initiation of therapy with **METSITAG** 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 **METSITAG** discontinued if evidence of renal impairment is present.

Hypoglycaemia

Patients receiving **METSITAG** 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.

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

Use of concomitant medications that may affect renal function or metformin disposition:

Concomitant medication(s) that may affect renal function or result in significant haemodynamic change or may interfere with the disposition of metformin, such as cationic medicines that are eliminated by renal tubular secretion (see section 4.5), should be used with caution.

Radiologic studies which involve the use of intravascular iodinated contrast materials (e.g. intravenous urogram, intravenous cholangiography, angiography and computed tomography (CT) scans with intravascular contrast materials: intravascular contrast studies with iodinated materials can lead to acute alteration of renal function, and have been associated with lactic acidosis in patients receiving metformin (see section 4.3). Therefore, in patients in whom any such study is planned, **METSITAG** should be temporarily discontinued at the time of or prior to the procedure and withheld for 48 hours following the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Hypoxic states:

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

Surgical procedures: Use of **METSITAG** should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids), and should not be restarted earlier than 48 hours following surgery or until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol intake:

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

Impaired hepatic function:

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

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

A patient with type 2 diabetes previously well controlled on **METSITAG** 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.

Bullous pemphigoid

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

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 **METSITAG** and temporarily administer insulin. **METSITAG** may be reinstituted after acute episode is resolved.

Paediatric use:

Safety and effectiveness of **METSITAG** in paediatric patients under 18 years have not been established.

4.5 Interaction with other medicines and other forms of interaction

METSITAG

Pharmacokinetic medicine interaction studies with **METSITAG** have not been performed, however such studies have been conducted with individual components of **METSITAG**, 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 agents

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

Sitagliptin phosphate:

In medicine interactions studies, sitagliptin did not have clinically meaningful effects on the pharmacokinetics of the following: Metformin, rosiglitazone, glyburide, simvastatin, warfarin and oral contraceptives. Based on these data, sitagliptin does not inhibit CYP Isoenzymes CYP3A4, 2CB or 2C9. Based on in vitro data, sitagliptin is also not expected to inhibit CYP2D6, 1A2, 2C19 or 2B6 or to induce CYP3A4 in patients with normal renal function.

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*.

Population pharmacokinetic analyses have been conducted in patients with type 2 diabetes. Concomitant medications did not have clinically meaningful effect sitagliptin pharmacokinetics. Medications assessed were those that are commonly administered to patients with type 2 diabetes including cholesterol-lowering medicines (e.g. statins, fibrates, ezetimibe), anti-platelet medicines (e.g. clopidogrel), antihypertensives (e.g. ACE inhibitors, angiotensin receptor blocker, beta-blocker, calcium

channel blockers, hydrochlorothiazide), analgesics and non-steroidal anti- inflammatory medicines (e.g. naproxen, diclofenac, celecoxib), anti-depressants. (e.g. bupropion, fluoxetine, sertraline), antihistamines (e.g. cetirizine), proton-pump inhibitors (e.g. omeprazole, lansoprazole), and medications for erectile dysfunction (e.g. sildenafil).

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

Metformin hydrochloride:

Glyburide: In a single-dose interaction study in type 2 diabetes patients, co- administrative 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 correction 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 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 metformin. Metformin had minimal effects on nifedipine.

Cationic medicines:

Cationic medicine (e.g. amiloride, digoxin, morphine, procainamide, quinidine, 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 interactions between metformin and oral cimetidine, have 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 **METSITAG** 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 contraceptive, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking medicines and isoniazid. When such medicines are administered to a patient receiving **METSITAG,** the patient should be closely observed to maintain adequate glycaemic control.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no well-controlled and adequate studies in pregnant women with **METSITAG** or its individual components; therefore, the safety of **METSITAG** in pregnant women is unknown. **METSITAG** should not be used during pregnancy.

Breastfeeding

No studies in lactating animals have been conducted with the combined active substances of **METSITAG**. **METSITAG** should not be used by a woman who is breastfeeding an infant (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

No studies of the effects of **METSITAG** on the ability to drive and use machines have been performed. **METSITAG** is not expected to affect the ability to drive and use machines. However, when driving or using machines, it should be considered that sitagliptin can cause dizziness and somnolence.

4.8 Undesirable effects

Summary of the safety profile

Tabulated summary of adverse reactions

Sitagliptin and metformin

System organ class	Frequency	Undesirable effect
Blood and lymphatic system disorders:	Less frequent	Thrombocytopenia
Immune system disorders:	Not known	Hypersensitivity reactions including anaphylactic responses
Metabolism and nutrition disorders:	Frequent	Hypoglycaemia
	Less frequent	Decreased Vitamin B_{12} and folic acid absorption with decrease of serum levels during long term use of metformin, lactic acidosis
Nervous system disorders	Frequent	Metallic taste
	Less frequent	Somnolence
	Not known	Headache, dizziness
Respiratory, thoracic and	Not known	Interstitial lung disease

mediastinal disorders:		
Gastrointestinal disorders:	Frequent	Nausea, flatulence, vomiting, loss of appetite
	Less frequent	Diarrhoea, constipation, upper abdominal pain
	Not known	Acute pancreatitis, fatal and non-fatal haemorrhagic and necrotizing pancreatitis
Skin and subcutaneous tissue disorders:	Less frequent	Pruritus, Mild erythema
	Not known	Angioedema, rash, urticaria, cutaneous vasculitis, exfoliative skin conditions including Stevens-Johnson syndrome, bullous pemphigoid.
Musculoskeletal and connective tissue disorders:	Not known	Arthralgia, myalgia, pain in extremity, back pain, arthropathy
Renal and urinary disorders:	Not known	Impaired renal function, acute renal failure.
Investigations	Less frequent	Decreased blood glucose level

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

Sitagliptin

In addition, in monotherapy studies of up to 24 weeks in duration of sitagliptin 100 mg once daily alone compared to placebo, adverse reactions considered as medicine-related reported in patients treated with sitagliptin in excess of that in patients receiving placebo are headache, hypoglycaemia, constipation and dizziness.

In addition to the medicine-related adverse reactions described above, adverse events (reported regardless of causal relationship to medicinal product) occurring in at least 5 % and more commonly in patients treated with sitagliptin, included upper respiratory tract infection and nasopharyngitis.

Additional adverse events that occurred more frequently in patients treated with sitagliptin (not reaching the 5 % level, but occurring with an incidence of greater than 0,5 % higher with sitagliptin than that in the control group), included osteoarthritis and pain in extremity.

Post-marketing data

During post-marketing experience of sitagliptin, one of the active substances of **METSITAG**, the following additional adverse reactions have been reported (frequency not known): Hypersensitivity

reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome (see “Section 4.4”); acute pancreatitis, including fatal and non- fatal haemorrhagic and necrotising pancreatitis (see “section 4.3”); worsening renal function, including acute renal failure (sometimes requiring dialysis); upper respiratory tract infection; nasopharyngitis; constipation, vomiting; headache.

Metformin

Established adverse reactions with metformin

The following side effects may occur with Metformin.

Metabolism and nutrition disorders

Less frequent: Decrease of vitamin B12 and folic acid absorption with decrease of serum levels during long-term use of metformin. This change is generally without clinical significance.

Less frequent: Lactic acidosis (see “section 4.8”).

Nervous system disorders

Frequent: Metallic taste.

Gastrointestinal disorders

Frequent: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These side effects occur most frequently during initiation of therapy and resolve spontaneously in most cases.

Skin and subcutaneous tissue disorders

Less frequent: Mild erythema in some hypersensitive individuals.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **Adverse drug reaction and quality reporting form**, found online under SAHPRA’s publications: https://.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form

4.9 Overdose

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

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.

Metformin hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycaemia was reported in approximately 10 % of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32 % of metformin overdose cases (see “section 4.3 and 4.8”). Metformin is dialysable with a clearance of up to 170 ml/min under good haemodynamic conditions. Therefore, haemodialysis may be useful for removal of accumulated medicine from patients in whom metformin overdosage is suspected.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.21.2 Oral Hypoglycaemics

Pharmacotherapeutic group: Drugs used in diabetes, Combinations of oral blood glucose lowering drugs.

ATC code: A10BD07

Mechanism of action

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

Sitagliptin Phosphate:

Sitagliptin phosphate is highly selective and potent inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme, and an orally active medicine, 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 highly selective and potent inhibitor of the enzyme DPP-4 and does not inhibit the closely related enzymes DPP-8 or DPP-9 at therapeutic concentrations. It differs in 4chemical 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.

Metformin hydrochloride:

Metformin is an antihyperglycaemic medicine, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanism of action is different from other classes of oral antihyperglycaemic medicines. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via three mechanism:

- by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- Modestly increasing insulin sensitivity in muscle, improving peripheral glucose uptake and utilisation
- Delaying absorption of intestinal glucose

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

Absorption

Sitagliptin phosphate:

The absolute bioavailability of sitagliptin is approximately 87 %. Co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food.

Metformin Hydrochloride:

The absolute bioavailability of a metformin hydrochloride 500 mg tablet approximately 50 to 60 % in healthy subjects when given under fasting conditions. After an oral dose of metformin, T_{max} is reached in 2,5 h, and the non-absorbed fraction recovered in faeces was 20-30 %.

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 phosphate:

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

Metformin Hydrochloride:

The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride tablets 850 mg averaged 654 ± 358 litre. Metformin is negligibly bound to plasma proteins, in contrast to sulphonylureas which are more than 90 % protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride tablets, steady-state plasma concentrations of metformin are reacted within 24 to 48 hours and are generally less than 1 mcg/ml. In the studies of metformin, maximum metformin plasma levels did not exceed 5 mcg/ml, even maximum doses.

Biotransformation

Sitagliptin Phosphate:

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

Metformin Hydrochloride:

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

Elimination

Sitagliptin Phosphate:

Following administration of an oral [14C] 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 t½ 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 suitable 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 dd not reduce the renal clearance of sitagliptin.

Metformin Hydrochloride:

Renal clearance is > 400 mL/min and approximately 3,5 times greater than creatinine clearance, indicating that metformin is eliminated by glomerular filtration and tubular secretion, the tubular secretion is a major route of metformin elimination. Following oral administration, approximately 90% of the absorbed medicine is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6,2 hours. In blood, the elimination half-life is approximately 17,6 hours, suggesting that the erythrocytes mass may be a compartment of distribution.

Special populations

Type 2 diabetes

Sitagliptin phosphate:

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

Metformin hydrochloride:

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

Renal impairment:

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

Sitagliptin phosphate:

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 compared to normal healthy control subjects. Because increases of this magnitude are not clinically relevant, dosage adjustment in these patients is not necessary. 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 hydrochloride:

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

Hepatic impairment

Sitagliptin phosphate:

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 hydrochloride:

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

Elderly

Sitagliptin Phosphate:

No dose adjustment is required based on age. Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on pharmacokinetics studies, elderly subjects between 65 to 80 years had approximately 19 % higher plasma concentrations of sitagliptin compared to younger subjects.

Metformin hydrochloride:

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

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

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 hydrochloride

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 anti-hyperglycaemic effect of metformin was comparable in males and females.

Body Mass Index (BMI)

Sitagliptin phosphate

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

Paediatric

Studies have not been performed in paediatric patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet contains: Microcrystalline cellulose, Povidone, Sodium lauryl sulfate, Croscarmellose Sodium, Sodium stearyl fumarate.

In addition, film-coating contains the following inactive ingredient: Hypromellose, Polyethylene glycol 400, Polyethylene glycol 6000, Talc, Titanium dioxide, Red iron oxide and Yellow iron oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in the original container at or below 25 °C.

Store in the original packaging and do not remove blisters from carton until required for use.

Keep out of reach of children.

6.5 Nature and contents of container

METSITAG tablets are packed in cold form (Alu-Alu) Blister pack and HDPE container pack.

Pack size: 10’s, 14’s, 28’s and 56’s tablets for Blister pack and 60’s for HDPE container pack.

Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

GROUND FLOOR, BLOCK 1,

BASSONIA ESTATE OFFICE PARK (EAST),

1 CUSSONIA DRIVE,

BASSONIA ROCK EXT 12

ALBERTON

GAUTENG

8. REGISTRATION NUMBERS

METSITAG 50/500: 56/21.2/0317

METSITAG 50/1000: 56/21.2/0318

9. DATE OF FIRST AUTHORISATION

21 November 2023

10. DATE OF REVISION OF THE TEXT

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PM0087-01

Vanita Rajool

Digitally signed by Vanita Rajool
DN: cn=Vanita Rajool, o=Macleods Pharmaceuticals SA (Pty) Ltd., ou=Responsible Pharmacist, email=vanitar@macleodspharma.com, c=ZA
Date: 2024.02.23 15:34:21 +02'00'