SCHEDULING STATUS

S3

1. NAME OF THE MEDICINAL PRODUCT

METPLITIN CO 50/850

METPLITIN CO 50/1 000

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

METPLITIN CO 50/850: Each tablet contains 50 mg sitagliptin hydrochloride monohydrate and 850 mg metformin hydrochloride.

METPLITIN CO 50/1 000: Each tablet contains 50 mg sitagliptin hydrochloride monohydrate and 1000 mg metformin hydrochloride.

METPLITIN CO is sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

METPLITIN CO 50/850: White coloured, bi-convex, oval tablets with "I" debossed on one side and plain on the other side.

METPLITIN CO 50/1 000: Brown coloured, biconvex, oval tablets with "7" debossed on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- METPLITIN CO 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.
- METPLITIN CO 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

General

The dosage of antihyperglycaemic therapy with METPLITIN CO 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.

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

Dosing Recommendations

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

50 mg sitagliptin/850 mg metformin hydrochloride

50 mg sitagliptin/1000 mg metformin hydrochloride

For patients switching from co-administration of sitagliptin and metformin

For patients switching from co-administration of sitagliptin and metformin, METPLITIN CO 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 METPLITIN CO 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).

No studies have been performed specifically examining the safety and efficacy of METPLITIN CO, in patients

previously treated with other oral antihyperglycaemic agents and switched to METPLITIN CO. 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

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

Elderly

As metformin and sitagliptin are excreted by the kidneys, METPLITIN CO 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 sections 4.4)

Paediatric Population

METPLITIN CO 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

METPLITIN CO is for oral use.

4.3 Contraindications

METPLITIN CO (sitagliptin hydrochloride monohydrate/metformin hydrochloride) is contraindicated in patients with:

- Known hypersensitivity to sitagliptin hydrochloride, metformin hydrochloride or any other component of METPLITIN CO (see section 6.1).
- Severe renal failure (GFR < 30 mL/min) (see section 4.4).
- Acute or chronic metabolic acidosis including diabetic ketoacidosis, with or without coma.
- Acute conditions with the potential to alter renal function such as:
  - ✓ dehydration,
  - ✓ severe infection,

- ✓ shock,
- ✓ intravascular administration of iodinated contrast agents (see section 4.4).

- Acute or chronic disease which may cause tissue hypoxia such as:
  - ✓ cardiac or respiratory failure,
  - ✓ recent myocardial infarction,
  - ✓ shock.
- Diabetic pre-coma.
- Hepatic impairment.
- Acute alcohol intoxication, alcoholism.
- Breastfeeding.

4.4 Special warnings and precautions for use

Acute pancreatitis

In post-marketing experience there have been reports of acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotising pancreatitis in patients taking sitagliptin. Patients should be informed of the characteristic symptom of acute pancreatitis: Persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of sitagliptin. If pancreatitis is suspected, METPLITIN CO and other potentially suspect medicinal products should be discontinued immediately.

Hypersensitivity Reactions

There have been post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of METPLITIN CO. 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 METPLITIN CO immediately, and institute an alternative class of medicines for treatment for diabetes.

Use in the elderly

As metformin and sitagliptin are excreted by the kidneys, METPLITIN CO 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.

METPLITIN CO

METPLITIN Co should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Monitoring of renal function

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

Hypoglycaemia in combination with a sulphonylurea

When sitagliptin, a component of METPLITIN CO was used in combination with metformin and a sulphonylurea, a medication known to cause hypoglycaemia, the incidence of sulphonylurea-induced hypoglycaemia was increased over that of placebo in combination with metformin and a sulphonylurea. Therefore, to reduce the risk of sulphonylurea-induced hypoglycaemia, a lower dose of sulphonylurea may be considered (see section 4.2). The use of METPLITIN CO in combination with insulin has not been studied.

Sitagliptin hydrochloride

Hypoglycaemia in combination with a sulphonylurea

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

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

Hypersensitivity reactions

There have been post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of METPLITIN CO. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to medicine exposure. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue METPLITIN CO, assess for other potential causes for the event, and institute alternative treatment for diabetes.

Bullous pemphigoid

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

Metformin hydrochloride

Lactic acidosis

Lactic acidosis is a rare, but serious metabolic complication that can occur due to metformin accumulation during treatment with METPLITIN CO (sitagliptin hydrochloride/metformin hydrochloride); when it occurs, it is fatal in approximately 50 % of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus and whenever there is significant tissue hypoperfusion and hypoxaemia. Lactic acidosis is characterised by elevated blood lactate levels (> 5 mmol/litre), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels greater than 5 mcg/ml are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0,03 cases/1 000 patient-years, with approximately 0,015 fatal cases/1 000 patient-years). In more than 20 000 patient-years exposure to metformin in 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. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radio contrast study and for any surgical procedure.

The onset of lactic acidosis often is subtle, and accompanied only by non-specific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence and non-specific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's medical practitioner must be aware of the possible importance of such symptoms and the patient should be instructed to notify the medical practitioner immediately if they occur. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels and even blood metformin levels may be useful. Once a patient is stabilised on any dose

level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be medicine related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/litre in patients taking metformin, do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonaemia).
Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the medicine should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialysable (with a clearance of up to 170 ml/min under good haemodynamic conditions), prompt haemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery (see section 4.3).

Hypoglycaemia

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

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

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

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

Hypoxic states

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

Surgical procedures

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

Alcohol intake

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

Impaired hepatic function

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

Vitamin B12 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 METPLITIN CO 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.

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

A patient with type 2 diabetes previously well controlled on METPLITIN CO, 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, METPLITIN CO must be stopped immediately and other appropriate corrective measures initiated.

Loss of control of blood glucose

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

Paediatric use

Safety and effectiveness of METPLITIN CO in paediatric patients under 18 years have not been established.

Use in the elderly

METPLITIN CO

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

Sitagliptin hydrochloride

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).

Metformin hydrochloride

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

Sitagliptin hydrochloride

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 WBC 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.

Metformin hydrochloride

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

4.5 Interaction with other medicines and other forms of interaction

METPLITIN CO

Pharmacokinetic medicine interaction studies with METPLITIN CO have not been performed; however, such studies have been conducted with the individual components of METPLITIN CO, 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

METPLITIN CO 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 medicinal products can adversely affect renal function, which may increase the risk of lactic acidosis, e.g., NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Concomitant use of medicines that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use. Close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when such products are 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 medicinal products. If necessary, the dose of the anti-hyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

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

Sitagliptin hydrochloride

In medicine interaction studies, sitagliptin did not have clinically meaningful effects on the pharmacokinetics of the following: Metformin, rosiglitazone, glyburide, simvastatin, warfarin and oral contraceptives. Based on these data, sitagliptin does not inhibit CYP isoenzymes CYP3A4, 2C8 or 2C9. Based on *in vitro* data,

sitagliptin is also not expected to inhibit CYP2D6, 1A2, 2C19 or 2B6 or to induce CYP3A4.

Population pharmacokinetic analyses have been conducted in patients with type 2 diabetes. Concomitant medications did not have a clinically meaningful effect on sitagliptin pharmacokinetics. Medications assessed were those that are commonly administered to patients with type 2 diabetes including cholesterol-lowering agents (e.g. statins, fibrates, ezetimibe), anti-platelet agents (e.g. clopidogrel), antihypertensives (e.g. ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, hydrochlorothiazide), analgesics and non- steroidal anti-inflammatory agents (e.g. naproxen, diclofenac, celecoxib), anti-depressants (e.g. bupropion, fluoxetine, sertraline), antihistamines (e.g. cetirizine), proton-pump inhibitors (e.g. omeprazole, lansoprozole), 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. 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-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 % 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 METPLITIN CO 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 METPLITIN CO, 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 and well-controlled studies in pregnant women with METPLITIN CO or its individual components; therefore, the safety of METPLITIN CO in pregnant women is not known.

METPLITIN CO is not recommended for use in pregnancy.

Breastfeeding

No studies in lactating animals have been conducted with the combined components of METPLITIN CO.

METPLITIN CO should not be used by a woman who is breastfeeding an infant.

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

METPLITIN CO 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 METPLITIN CO is used in combination with a sulphonylurea or with insulin.

4.8 Undesirable effects

Summary of the safety profile

Serious adverse reactions including pancreatitis and hypersensitivity reactions have been reported.

Hypoglycaemia has been reported in combination with sulphonylurea (13,8 %) and insulin (10,9 %).

Sitagliptin and metformin

Tabulated summary of adverse reactions

Adverse drug reactions are classified by system organ class and frequency; within each frequency grouping, and listed in the table below.

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

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

*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 medicinal products than in studies of sitagliptin and metformin alone. These included hypoglycaemia (frequency very common with sulphonylurea or insulin), constipation (common with sulphonylurea), peripheral oedema (common with pioglitazone), and headache and dry mouth (uncommon with insulin).

Sitagliptin

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

Among these patients, adverse events reported regardless of causal relationship to medicinal product occurring in at least 5 % included upper respiratory tract infection and nasopharyngitis. In addition, osteoarthritis and pain in extremity were reported with frequency uncommon (> 0,5 % higher among sitagliptin users than that in the control group).

Metformin

Gastrointestinal symptoms were reported very commonly in clinical studies and post-marketing use of metformin.

Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases. Additional adverse reactions associated with metformin include metallic taste (common); lactic acidosis, liver function disorders, hepatitis, urticaria, erythema, and pruritus (very rare). Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B12 deficiency (e.g., megaloblastic anaemia).

Frequency categories are based on information available from metformin Summary of Product Characteristics available in the EU.

Paediatric population

In clinical trials with the combination of sitagliptin/metformin in paediatric patients with type 2 diabetes mellitus

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

TECOS Cardiovascular Safety Study

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7,332 patients treated with sitagliptin, 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and < 50 mL/min/1.73 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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Sitagliptin hydrochloride

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were generally well tolerated. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin (see section 5.1, PHARMACOLOGICAL ACTION, Pharmacodynamics, Cardiac electrophysiology"). There is no experience with doses above 800 mg in humans. 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 10 days and 400 mg per day for periods of up to 28 days.

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

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

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

Sitagliptin hydrochloride

Sitagliptin hydrochloride is an orally-active, potent and selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. The DPP-4 inhibitors are a class of agents that act as incretin

enhancers. By inhibiting the DPP-4 enzyme, sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production.

Metformin hydrochloride

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

5.2 Pharmacokinetic properties

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

Absorption

Sitagliptin hydrochloride

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

Metformin hydrochloride

Studies using single oral doses of metformin hydrochloride tablets 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alternation in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40 % lower mean peak plasma concentration (C_{max}), a 25 % lower area under the plasma concentration vs. time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Sitagliptin hydrochloride

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

Metformin hydrochloride

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

Biotransformation

Sitagliptin hydrochloride

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.

Metformin hydrochloride

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

Elimination

Sitagliptin hydrochloride

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 and 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.

Metformin hydrochloride

Renal clearance is approximately 3,5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90 % of the absorbed medicine is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6,2 hours. In blood the elimination half-life is approximately 17,6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special populations

Type 2 diabetes

Sitagliptin hydrochloride

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

Metformin hydrochloride

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

Renal insufficiency

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

Sitagliptin hydrochloride

An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate

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

Metformin hydrochloride

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

Hepatic insufficiency

Sitagliptin hydrochloride

In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), mean AUC and C_{max} of sitagliptin increased approximately 21 % and 13 %, respectively, compared to healthy matched controls following administration of a single 100 mg dose of sitagliptin hydrochloride. These differences are not considered to be clinically meaningful.

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

Metformin hydrochloride

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

Gender

Sitagliptin hydrochloride

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 antihyperglycaemic effect of metformin was comparable in males and females.

Elderly

Sitagliptin hydrochloride

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 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, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see Metformin package insert).

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, Metformin hydrochloride).

Paediatric

No studies have been performed in paediatric patients.

Body Mass Index (BMI)

Sitagliptin hydrochloride

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Magnesium stearate

Microcrystalline cellulose

Povidone (PVP K30)

Purified Water

Sodium lauryl sulphate

Film-coating

50/850 mg:

Opadry II White 85F580019 contains:

Macrogol/PEG

Polyvinyl alcohol-part, hydrolysed

Talc

Titanium dioxide

50/1000 mg:

Opadry-II Brown 85F565140 contains:

Iron oxide red

Iron oxide yellow

Macrogol/PEG

Polyvinyl alcohol-part, hydrolysed

Talc

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 ºC.

Keep out of reach of children.

Keep the tablets in the blisters and the blisters in the outer carton until required for use.

6.5 Nature and contents of container

METPLITIN CO are packed in OPA/Alu/PVC-Alu blisters in packs of 30 or 60 tablets with blisters containing

10 tablets.

Not all strengths and pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8. REGISTRATION NUMBERS

METPLITIN CO 50/850: 56/21.2/0994

METPLITIN CO 50/1 000: 56/21.2/0995

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01 October 2024

10. DATE OF REVISION OF TEXT