SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

GLINSIP-M 50/500 (Sitagliptin and metformin Hydrochloride Tablets 50mg / 500 mg).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sitagliptin and metformin Hydrochloride Tablets 50mg / 500 mg

Each tablet contains, Sitagliptin 50 mg, Equivalent to Sitagliptin phosphate 62.033mg, Metformin Hydrochloride USP 500mg.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated Tablets

Sitagliptin and metformin Hydrochloride Tablets 50mg / 500 mg

White, capsule -shaped, film coated tablet with "27" debossed on one side and "V1" on other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

For adult patients with type 2 diabetes mellitus:

Sitagliptin and metformin Hydrochloride is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin.

Sitagliptin and metformin Hydrochloride is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.

Sitagliptin and metformin Hydrochloride is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist.

Sitagliptin and metformin Hydrochloride is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control.

4.2 Posology and Method of

administration Posology

The dose of antihyperglycaemic therapy with Sitagliptin and metformin Hydrochloride 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.

Adults with normal renal function (GFR ≥ 90 mL/min)

For patients inadequately controlled on maximal tolerated dose of metformin monotherapy

For patients not adequately controlled on metformin alone, the usual starting dose should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken.

For patients switching from co-administration of sitagliptin and metformin

For patients switching from co-administration of sitagliptin and metformin, Sitagliptin and metformin Hydrochloride should be initiated at the dose of sitagliptin and metformin already being taken.

For patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a sulphonylurea

The dose should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Sitagliptin and metformin Hydrochloride is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be required to reduce the risk of hypoglycaemia.

For patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a PPARγ agonist

The dose should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken.

For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin

The dose should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Sitagliptin and metformin Hydrochloride is used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycaemia.

For the different doses on metformin, Sitagliptin and metformin Hydrochloride is available in strengths of 50 mg sitagliptin and 850 mg metformin hydrochloride or 1,000 mg metformin hydrochloride.

All patients should continue their recommended diet with an adequate distribution of carbohydrate intake during the day.

Special populations

Renal impairment

No dose adjustment is needed for patients with mild renal impairment (glomerular filtration rate [GFR] ≥ 60 mL/min). A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin in patients with GFR < 60 mL/min.

If no adequate strength of Sitagliptin and metformin Hydrochloride is available, individual monocomponents should be used instead of the fixed-dose combination.

GFR mL/min	Metformin	Sitagliptin
60-89	Maximum daily dose is 3,000 mg. Dose reduction may be considered in relation to declining renal function	Maximum daily dose is 100 mg.
45-59	Maximum daily dose is 2,000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 100 mg.
30-44	Maximum daily dose is 1,000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 50 mg.
< 30	Metformin is contraindicated.	Maximum daily dose is 25 mg.

Hepatic impairment

Sitagliptin and metformin Hydrochloride must not be used in patients with hepatic impairment.

Elderly

As metformin and sitagliptin are excreted by the kidney, Sitagliptin and metformin Hydrochloride 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 4.3 and 4.4).

Paediatric population

Sitagliptin and metformin Hydrochloride should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy. Currently available data are described in sections 4.8, 5.1, and

5.2. Sitagliptin and metformin Hydrochloride has not been studied in paediatric patients under 10 years of age.

Method of administration

Sitagliptin and metformin Hydrochloride should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin.

4.3. Contraindications

Sitagliptin and metformin Hydrochloride is contraindicated in patients with:

- hypersensitivity to the active substances or to any of the excipients

- any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis);

- diabetic pre-coma;

- severe renal failure (GFR< 30 mL/min)

- 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;

- hepatic impairment;

- acute alcohol intoxication, alcoholism;

- breast-feeding.

4.4. Special warnings and precautions for use

General

Sitagliptin and metformin Hydrochloride should not be used in patients with type 1 diabetes and must not be used for the treatment of diabetic ketoacidosis.

Acute pancreatitis

Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of sitagliptin (with or without supportive treatment), but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, Sitagliptin and metformin

Hydrochloride and other potentially suspect medicinal products should be discontinued; if acute pancreatitis is confirmed, Sitagliptin and metformin

Hydrochloride should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Lactic acidosis

Lactic acidosis, a rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis.

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.

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

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 (> 5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

Renal function

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

Hypoglycaemia

Patients receiving Sitagliptin and metformin Hydrochloride in combination with a sulphonylurea or with insulin may be at risk for hypoglycaemia. Therefore, a reduction in the dose of the sulphonylurea or insulin may be necessary.

Hypersensitivity reactions

Post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin have been reported. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the

first dose. If hypersensitivity reaction is suspected, Sitagliptin and metformin Hydrochloride should be discontinued, other potential causes of the event should be assessed, and alternative treatment for diabetes should be instituted

Bullous pemphigoid

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

Sitagliptin and metformin Hydrochloride should be discontinued.

Surgery

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

Administration of iodinated contrast agent

Intravascular administration of iodinated contrast agents may lead to contrastinduced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Sitagliptin and metformin Hydrochloride should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

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

A patient with type 2 diabetes previously well controlled on Sitagliptin and metformin Hydrochloride 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.

Vitamin B12 Deficiency

Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anaemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

Sodium

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

4.5. Interaction with other medicinal products and other forms of interaction

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

Pharmacokinetic drug interaction studies with Sitagliptin and metformin Hydrochloride have not been performed; however, such studies have been conducted with the individual active substances, sitagliptin and metformin.

Concomitant use not recommended

Alcohol

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

Iodinated contrast agents

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

Combinations requiring precautions for use

Some medicinal products can adversely affect renal function, which may increase the risk of lacti 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 medicinal products that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis.

Consider the benefits and risks of concomitant use. Close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when such products are coadministered.

Glucocorticoids (given by systemic and local routes) beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed

and more frequent blood glucose monitoring performed, especially at the beginning of treatment with such medicinal products. If necessary, the dose of the antihyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

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

Effects of other medicinal products on sitagliptin

In vitro and clinical data described below suggest that the risk for clinically meaningful interactions following co-administration of other medicinal products is low.

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

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

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

Effects of sitagliptin on other medicinal products

Digoxin: Sitagliptin had a small effect on plasma digoxin concentrations. Following administration of

0.25 mg digoxin concomitantly with 100 mg of sitagliptin daily for 10 days, the plasma AUC o digoxin was increased on average by 11 %, and the plasma Cmax on average by 18 %. No dose adjustment of digoxin is recommended. However, patients at risk of digoxin toxicity should be monitored for this when sitagliptin and digoxin are administered concomitantly.

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

4.6. Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of sitagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses of sitagliptin.

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

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

Breast-feeding

No studies in lactating animals have been conducted with the combined active substances of this medicinal product. In studies performed with the individual active substances, both sitagliptin and metformin are excreted in the milk of lactating rats. Metformin is excreted in human milk in small amounts. It is not known whether sitagliptin is excreted in human milk. Sitagliptin and metformin Hydrochloride must therefore not be used in women who are breast-feeding.

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

Sitagliptin and metformin Hydrochloride 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 Sitagliptin and metformin Hydrochloride is used in combination with a sulphonylurea or with insulin.

4.8. Undesirable effects

Summary of the safety profile

There have been no therapeutic clinical studies conducted with Sitagliptin and metformin Hydrochloride tablets however bioequivalence of Sitagliptin and metformin Hydrochloride with co- administered sitagliptin and metformin has been demonstrated (see section 5.2). Serious adverse reactions including pancreatitis and hypersensitivity reactions have been reported. Hypoglycaemia has been reported in combination with sulphonylurea (13.8 %) and insulin (10.9 %).

Tabulated list of adverse reactions

Sitagliptin and metformin

Adverse reactions are listed below as MedDRA preferred term by system organ class and absolute frequency (Table 1). Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (cannot be estimated from the available data).

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	Rare

Immune system disorders

hypersensitivity reactions including anaphylactic responses*,†	Frequency not known
Metabolism and nutrition disorders	
hypoglycaemia†	Common
Vitamin B12 decrease/deficiency†	Common
Nervous system disorders	
somnolence	Uncommon
Respiratory, thoracic and mediastinal disorders	
interstitial lung disease*	Frequency not known
Gastrointestinal disorders	
diarrhoea	Uncommon
nausea	Common
flatulence	Common
constipation	Uncommon
upper abdominal pain	Uncommon
vomiting	common
acute pancreatitis*,†,‡	Frequency not known
fatal and non-fatal haemorrhagic and necrotizing pancreatitis*,†	Frequency not known
Skin and subcutaneous tissue disorders	
pruritus*	Uncommon

angioedema*,†	Frequency not known
rash*,†	Frequency not known
urticaria*,†	Frequency not known
cutaneous vasculitis*,†	Frequency not known
exfoliative skin conditions including	Frequency not known

Stevens-Johnson syndrome*,†

bullous pemphigoid*	Frequency not known
Musculoskeletal and connective tissue disorders	
arthralgia*	Frequency not known
myalgia*	Frequency not known
pain in extremity*	Frequency not known
back pain*	Frequency not known
arthropathy*	Frequency not known
Renal and urinary disorders	
impaired renal function*	Frequency not known
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 postmarketing 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). Frequency categories are based on information available from metformin Summary of Product Characteristics available in the EU.

Paediatric population

In clinical studies with Sitagliptin and metformin Hydrochloride 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 m2), 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 of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board,

Pharmacovigilance Electronic Reporting System (PvERS)

https://pv.pharmacyboardkenya.org

4.9. Overdose

During controlled clinical studies in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin.

There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

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

In clinical studies, approximately 13.5 % of the dose was removed over a 3- to 4hour haemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Medicinal products used in diabetes, Combinations of oral blood glucose lowering medicinal products, ATC code: A10BD07

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

Sitagliptin

Mechanism of action

Sitagliptin phosphate is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. The DPP-4 inhibitors are a class of 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. When blood glucose levels are low, insulin release is not enhanced and glucagon secretion is not suppressed.

Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations. Sitagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulphonylureas or meglitinides, biguanides, peroxisome proliferator-activated receptor gamma (PPARγ) agonists, alpha- glucosidase inhibitors, and amylin analogues.

In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Co- administration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations.

Clinical efficacy and safety

Overall, sitagliptin improved glycaemic control when used as monotherapy or in combination treatment in adult patients with type 2 diabetes.

In clinical studies, sitagliptin as monotherapy improved glycaemic control with significant reductions in haemoglobin A1c (HbA1c) and fasting and postprandial glucose. Reduction in fasting plasma glucose (FPG) was observed at 3 weeks, the first time point at which FPG was measured. The observed incidence of hypoglycaemia in patients treated with sitagliptin was similar to placebo. Body weight did not increase from baseline with sitagliptin therapy. Improvements in surrogate markers of beta cell function, including HOMA-β (Homeostasis Model

Assessment-β), proinsulin to insulin ratio, and measures of beta cell responsiveness from the frequently-sampled meal tolerance test were observed.

Studies of sitagliptin in combination with metformin

In a 24-week, placebo-controlled clinical study to evaluate the efficacy and safety of the addition of sitagliptin 100 mg once daily to ongoing metformin, sitagliptin provided significant improvements in glycaemic parameters compared with placebo. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo. In this study there was a similar incidence of hypoglycaemia reported for patients treated with sitagliptin or placebo.

In a 24-week placebo-controlled factorial study of initial therapy, sitagliptin 50 mg twice daily in combination with metformin (500 mg or 1,000 mg twice daily) provided significant improvements in glycaemic parameters compared with either monotherapy. The decrease in body weight with the combination of sitagliptin and metformin was similar to that observed with metformin alone or placebo; there was no change from baseline for patients on sitagliptin alone. The incidence of hypoglycaemia was similar across treatment groups.

Study of sitagliptin in combination with metformin and a sulphonylurea

A 24-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to glimepiride (alone or in combination with metformin). The addition of sitagliptin to glimepiride and metformin provided significant improvements in glycaemic parameters. Patients treated with sitagliptin had a modest increase in body weight (+1.1 kg) compared to those given placebo.

Study of sitagliptin in combination with metformin and a PPARγ agonist

A 26-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to the combination of pioglitazone and metformin. The addition of sitagliptin to pioglitazone and metformin provided significant improvements in glycaemic parameters. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo. The incidence of hypoglycaemia was also similar in patients treated with sitagliptin or placebo.

Study of sitagliptin in combination with metformin and insulin

A 24-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to insulin (at a stable dose for at least 10 weeks) with or without metformin (at least 1,500 mg). In patients taking pre-mixed insulin, the mean daily dose was 70.9 U/day. In patients taking nonpre-mixed (intermediate/long-acting) insulin, the mean daily dose was 44.3 U/day. Data from the 73 % of patients who were taking metformin are presented in Table 2. The addition of sitagliptin to insulin provided significant improvements in glycaemic parameters. There was no meaningful change from baseline in body weight in either group.

Table 2: HbA1c results in placebo-controlled combination therapy studies of

sitagliptin and metformin*

Study	Mean baseline HbA1c (%)	Mean change from baseline HbA1c (%)	Placebo-corrected mean change in HbA1c (%) (95 % CI)
Sitagliptin 100 mg once daily added to ongoing metformin therapy‖ ‖ (N=453)	8.0	-0.7†	-0.7†,‡ (-0.8, -0.5)
Sitagliptin 100 mg once daily added to ongoing glimepiride + metformin therapy‖ ‖ (N=115)	8.3	-0.6†	-0.9†,‡ (-1.1, -0.7)
Sitagliptin 100 mg once daily added to ongoing pioglitazone + metformin therapy¶ (N=152)	8.8	-1.2†	-0.7†,‡ (-1.0, -0.5)
Sitagliptin 100 mg	8.7	-0.7§	-0.5§,‡ (-0.7, -0.4)

once daily added to ongoing insulin + metformin therapy ‖ ‖ (N=223)			
Initial Therapy (twice daily) ‖ ‖ : Sitagliptin 50 mg + metformin 500 mg (N=183)	8.8	-1.4†	-1.6†,‡ (-1.8, -1.3)
Initial Therapy (twice daily) ‖ ‖ : Sitagliptin 50 mg + metformin 1,000 mg (N=178)	8.8	-1.9†	-2.1†,‡ (-2.3, -1.8)

* All Patients Treated Population (an intention-to-treat analysis).

† Least squares means adjusted for prior antihyperglycaemic therapy status and baseline value.

‡ p< 0.001 compared to placebo or placebo + combination treatment.

‖ ‖ HbA1c (%) at week 24.

¶ HbA1c (%) at week 26.

§ Least squares mean adjusted for insulin use at Visit 1 (pre-mixed vs. non-premixed [intermediate- or long-acting]), and baseline value.

In a 52-week study, comparing the efficacy and safety of the addition of sitagliptin 100 mg once daily or glipizide (a sulphonylurea) in patients with inadequate glycaemic control on metformin monotherapy, sitagliptin was similar to glipizide in reducing HbA1c (-0.7 % mean change from baselines at week 52, with baseline HbA1c of approximately 7.5 % in both groups). The mean glipizide dose used in the comparator group was 10 mg per day with approximately 40 % of patients requiring a glipizide dose of < 5 mg/day throughout the study.

However, more patients in the sitagliptin group discontinued due to lack of efficacy than in the glipizide group. Patients treated with sitagliptin exhibited a significant mean decrease from baseline in body weight (-1.5 kg) compared to a significant weight gain in patients administered glipizide (+1.1 kg). In this study, the proinsulin to insulin ratio, a marker of efficiency of insulin synthesis and release, improved with sitagliptin and deteriorated with glipizide treatment. The incidence of hypoglycaemia in the sitagliptin group (4.9 %) was significantly lower than that in the glipizide group (32.0 %).

A 24-week placebo-controlled study involving 660 patients was designed to evaluate the insulin- sparing efficacy and safety of sitagliptin (100 mg once daily) added to insulin glargine with or without metformin (at least 1,500 mg) during intensification of insulin therapy. Among patients taking metformin, baseline HbA1c was 8.70 % and baseline insulin dose was 37 IU/day. Patients were instructed to titrate their insulin glargine dose based on fingerstick fasting glucose values. Among patients taking metformin, at Week 24, the

increase in daily insulin dose was 19 IU/day in patients treated with sitagliptin and 24

IU/day in patients treated with placebo. The reduction in HbA1c for patients treated with sitagliptin, metformin, and insulin was -1.35 % compared to -0.90 % for patients treated with placebo, metformin, and insulin, a difference of -0.45 % [95 % CI: -0.62, -0.29]. The incidence of hypoglycaemia was 24.9 % for patients treated with sitagliptin, metformin, and insulin and 37.8 % for patients treated with placebo, metformin, and insulin. The difference was mainly due to a higher percentage of patients in the placebo group experiencing 3 or more episodes of hypoglycaemia (9.1 vs. 19.8 %). There was no difference in the incidence of severe hypoglycaemia.

Metformin

Mechanism of action

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via three mechanisms:

- by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis

- in muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and Utilization

- by delaying intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

Clinical efficacy and safety

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDLc and triglyceride levels.

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient- years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patientyears), p=0.0034

- a significant reduction of the absolute risk of any diabetes-related mortality: metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p=0.017

- a significant reduction of the absolute risk of overall mortality: metformin

13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years, (p=0.011), andversus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years (p=0.021)

- a significant reduction in the absolute risk of myocardial infarction:

metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patientyears, (p=0.01).

The TECOS was a randomised study in 14,671 patients in the intention-to-treat population with an HbA1c of ≥ 6.5 to 8.0 % with established CV disease who received sitagliptin (7,332) 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and < 50 mL/min/1.73 m2) or placebo (7,339) added to usual care targeting regional standards for HbA1c and CV risk factors. Patients with an eGFR < 30 mL/min/1.73 m2 were not to be enrolled in the study. The study population included 2,004 patients ≥ 75 years of age and 3,324 patients with renal impairment (eGFR < 60 mL/min/1.73 m2). Over the course of the study, the overall estimated mean (SD) difference in HbA1c between the sitagliptin and placebo groups was 0.29 % (0.01), 95 % CI (-0.32, -0.27); p < 0.001.

The primary cardiovascular endpoint was a composite of the first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for unstable angina. Secondary cardiovascular endpoints included the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; first occurrence of the individual components of the primary composite; all-cause mortality; and hospital admissions for congestive heart failure. After a median follow up of 3 years, sitagliptin, when added to usual care, did not increase the risk of major adverse cardiovascular events or the risk of hospitalisation for heart failure compared to usual care without sitagliptin in patients with type 2 diabetes (Table 3).

Table 3: Rates of Composite Cardiovascular Outcomes and Key Secondary Outcomes

	Sitagliptin 100 mg		Placebo			
	N (%)	Incidence rate per 100 patient years*	N (%)	Incidence rate per 100 Patient years*	Hazard Ratio N (%) (95 % CI)	p-value†
Analysis in the Intention-to-Treat Population						

Number of patients	7,332		7,339		0.98 (0.89–1.08)	<0.001
Primary Composite Endpoint (Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for unstable angina)	839 (11.4)	4.1	851 (11.6)	4.2		
Secondary Composite Endpoint (Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke)	745 (10.2)	3.6	746 (10.2)	3.6	0.99 (0.89–1.10)	<0.001
Secondary Outcome						
Cardiovascular death	380 (5.2)	1.7	366 (5.0)	1.7	1.03 (0.89-1.19)	0.711
All myocardial infarction (fatal and non-fatal)	300 (4.1)	1.4	316 (4.3)	1.5	0.95 (0.81–1.11)	0.487
All stroke (fatal and non-fatal)	178 (2.4)	0.8	183 (2.5)	0.9	0.97 (0.79–1.19)	0.760
Hospitalisation for unstable angina	116 (1.6)	0.5	129 (1.8)	0.6	0.90 (0.70–1.16)	0.419
Death from any cause	547 (7.5)	2.5	537 (7.3)	2.5	1.01 (0.90–1.14)	0.875
Hospitalisation for hear t failure‡	228 (3.1)	1.1	229 (3.1)	1.1	1.00 (0.83–1.20)	0.983

* Incidence rate per 100 patient-years is calculated as 100 × (total number of patients with ≥ 1 event during eligible exposure period per total patient-years of follow-up).

† Based on a Cox model stratified by region. For composite endpoints, the p-values correspond to a test of non-inferiority seeking to show that the hazard

ratio is less than 1.3. For all other endpoints, the p-values correspond to a test of differences in hazard rates.

‡ The analysis of hospitalisation for heart failure was adjusted for a history of heart failure at baseline. Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Sitagliptin and metformin Hydrochloride in all subsets of the paediatric population in type 2 diabetes mellitus.

The safety and efficacy of the addition of sitagliptin in paediatric patients aged 10 to 17 years with type 2 diabetes and inadequate glycaemic control on metformin with or without insulin was assessed in two studies over 54 weeks. The addition of sitagliptin (administered as sitagliptin + metformin or sitagliptin + metformin extended release (XR)) was compared to the addition of placebo to metformin or metformin XR.

While superiority of HbA1c reduction was demonstrated for sitagliptin + metformin / sitagliptin + metformin XR over metformin at Week 20 in the pooled analysis of these two studies, results from the individual studies were inconsistent. Furthermore, greater efficacy for sitagliptin + metformin / sitagliptin + metformin XR compared to metformin was not observed at Week 54. Therefore, Sitagliptin and metformin Hydrochloride should not be used in paediatric patients aged 10 to 17 years old because of insufficient efficacy.

5.2. Pharmacokinetic properties

Sitagliptin and metformin Hydrochloride A bioequivalence study in healthy subjects demonstrated that the Sitagliptin and metformin Hydrochloride (sitagliptin/metformin hydrochloride) combination tablets are bioequivalent to coadministration of sitagliptin phosphate and metformin hydrochloride as individual tablets.

The following statements reflect the pharmacokinetic properties of the individual active substances of Sitagliptin and metformin Hydrochloride.

Sitagliptin

Absorption

Following oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median Tmax) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8.52 M•hr, Cmax was 950 nM. The absolute bioavailability of sitagliptin is approximately 87 %. Since coadministration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food.

Plasma AUC of sitagliptin increased in a dose-proportional manner. Doseproportionality was notestablished for Cmax and C24hr (Cmax increased in a greater than dose-proportional manner and C24hr increased in a less than dose-proportional manner).

Distribution

The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 litres.

The fraction of sitagliptin reversibly bound to plasma proteins is low (38 %).

Biotransformation

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

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

Elimination

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 substrate for human organic anion tranporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, ciclosporin, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin. Sitagliptin is not a substrate for OCT2 or OAT1 or PEPT1/2 transporters. In vitro, sitagliptin did not inhibit OAT3 (IC50=160 (cid:0)(cid:0)(cid:0)(cid:0)(cid:0)(cid:0)(cid:0)M) or p-glycoprotein (up to 250 (cid:0)(cid:0)(cid:0)(cid:0)(cid:0)(cid:0)(cid:0)M) mediated transport at therapeutically relevant plasma concentrations. In a clinical study sitagliptin had a small effect on plasma digoxin concentrations indicating that sitagliptin may be a mild inhibitor of p-glycoprotein.

Characteristics in patients

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

Renal impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of a reduced dose of sitagliptin (50 mg) in patients with varying degrees of chronic renal impairment compared to normal healthy control subjects. The study included patients with mild, moderate, and severe renal impairment, as well as patients with ESRD on haemodialysis. In addition, the effects of renal impairment on sitagliptin pharmacokinetics in patients with type 2 diabetes and mild, moderate, or severe renal impairment (including ESRD) were assessed using population pharmacokinetic analyses. Compared to normal healthy control subjects, plasma AUC of sitagliptin was increased by approximately 1.2-fold and 1.6-fold in patients with mild renal impairment (GFR ≥ 60 to < 90 mL/min) and patients with moderate renal impairment (GFR ≥ 45 to < 60 mL/min), respectively.

Because increases of this magnitude are not clinically relevant, dose adjustment in these patients is not necessary.

Plasma AUC of sitagliptin was increased approximately 2-fold in patients with moderate renal impairment (GFR ≥ 30 to < 45 mL/min), and approximately 4-fold in patients with severe renal impairment (GFR < 30 mL/min), including patients with ESRD on haemodialysis. Sitagliptin was modestly removed by haemodialysis (13.5 % over a 3- to 4-hour haemodialysis session starting 4 hours post-dose).

Hepatic impairment

No dose adjustment for sitagliptin is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score (cid:0)(cid:0)(cid:0)(cid:0)(cid:0)(cid:0)(cid:0) 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.

Elderly

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

Paediatric population

The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in paediatric patients (10 to 17 years of age) with type 2 diabetes. In this population, the dose adjusted AUC of sitagliptin in plasma was approximately 18 % lower compared to adult patients with type 2 diabetes for a 100 mg dose. No studies with sitagliptin have been performed in paediatric patients < 10 years of age.

Other patient characteristics

No dose adjustment is necessary based on gender, race, or body mass index (BMI). These characteristics 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

Absorption

After an oral dose of metformin, Tmax is reached in 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60 % in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30 %.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 µg/mL. In controlled clinical studies, maximum metformin plasma levels (Cmax) did not exceed 5 µg/mL, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40 % lower plasma peak concentration, a 25 % decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.

Distribution

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

Biotransformation

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

Elimination

Renal clearance of metformin is > 400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

5.3. Preclinical safety data

No animal studies have been conducted with Sitagliptin and metformin Hydrochloride. In 16-week studies in which dogs were treated with either metformin alone or a combination of metformin and sitagliptin, no additional toxicity was observed from the combination. The NOEL in these studies was observed at exposures to sitagliptin of approximately 6 times the human exposure nd to metformin of approximately 2.5 times the human exposure.

The following data are findings in studies performed with sitagliptin or metformin individually.

Sitagliptin

Renal and liver toxicity were observed in rodents at systemic exposure values 58 times the human exposure level, while the no-effect level was found at 19 times the human exposure level. Incisor teeth abnormalities were observed in rats at exposure levels 67 times the clinical exposure level; the no- effect level for this finding was 58-fold based on the 14-week rat study. The relevance of these findings for humans is unknown. Transient treatment-related physical signs, some of which suggest neural toxicity, such as open-mouth breathing, salivation, white foamy emesis, ataxia, trembling, decreased activity, and/or hunched posture were observed in dogs at exposure levels approximately 23 times the clinical exposure level. In addition, very slight to slight skeletal muscle degeneration was also observed histologically at doses resulting in systemic exposure levels of approximately 23 times the human exposure level. A no-effect level for these findings was found at an exposure 6-fold the clinical exposure level.

Sitagliptin has not been demonstrated to be genotoxic in preclinical studies. Sitagliptin was not carcinogenic in mice. In rats, there was an increased incidence of hepatic adenomas and carcinomas at systemic exposure levels 58 times the human exposure level. Since hepatotoxicity has been shown to correlate with induction of hepatic neoplasia in rats, this increased incidence of hepatic tumours in rats was likely secondary to chronic hepatic toxicity at this high dose. Because of the high safety margin (19-fold at this no-effect level), these neoplastic changes are not considered relevant for the situation in humans.

No treatment related effects on fertility were observed in male and female rats given sitagliptin prior to and throughout mating.

In a pre-/post-natal development study performed in rats sitagliptin showed no adverse reactions. Reproductive toxicity studies showed a slight treatment-related increased incidence of foetal rib malformations (absent, hypoplastic and wavy ribs) in the offspring of rats at systemic exposure levels more than 29 times the human exposure levels. Maternal toxicity was seen in rabbits at more than 29 times the human exposure levels. Because of the high safety margins, these findings do not suggest a relevant risk for human reproduction. Sitagliptin is secreted in considerable amounts into the milk of lactating rats (milk/plasma ratio: 4:1).

Metformin

Preclinical data for metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients:

Microcrystalline Cellulose,

Sodium lauryl sulfate,

Povidone K 90,

Sodium stearyl fumarate,

Composition of Opadry II white 85F18422:

polyvinyl alcohol-part hydrolysed,

Titanium dioxide, macro-OL/PE,

Talc

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 Months

6.4. Special precautions for storage

Store below 30ºC.

Store below 30°C.

6.5 Nature and contents of pack's

10's Alu-Alu Blister pack 10's white Opaque PVC/PE/PVDC- Alu blister pack.

6.6 Instructions for use, handling and disposal

Any unused medicinal product or waste material should be disposed of in accordance with local Requirements

7. MARKETING AUTHORISATION HOLDER

Hetero Labs Limited.

7-2-A2 Hetero Corporate Industrial Estates Sanath Nagar Hyderabad-500 018 Andhra pradesh India.

8. MARKETING AUTHORISATION NUMBER(S)

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