Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Name: Lino-M 500 Tablet

Linagliptin INN 2.5 mg and Metformin hydrochloride BP 500 mg.

2. Qualitative and quantitative composition

Each film coated tablet contains Linagliptin INN 2.5 mg and Metformin hydrochloride BP 500 mg

For the full list of expedients, see section 6.1.

3. Pharmaceutical form

Tablet

Light, orange, caplet, bi-convex film coated tablets, one side debossed with "ACME" and the other side debossed with break-line

4. Clinical particulars

4.1 Therapeutic indications

LINO-M tablets are indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate.

4.2 Posology and method of administration

Posology

Recommended starting dose

In patients currently not treated with metformin, initiate treatment with 2.5 mg linagliptin/500 mg metformin hydrochloride twice daily

In patients already treated with metformin, start with 2.5 mg linagliptin and the current dose of metformin hydrochloride twice daily.

Patients already treated with linagliptin and metformin individual components may be switched to

LINO-M containing the same doses of each component.

Patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a sulphonyl urea

The dose of LINO-M should provide linagliptin dosed as 2.5 mg twice daily (5 mg total daily dose) and a dose of metformin similar to the dose already being taken. When linagliptin plus metformin hydrochloride is used in combination with a sulphonyl urea, a lower dose of the sulphonyl urea may be required to reduce the risk of hypoglycaemia (see section 4.4).

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

The dose of LINO-M should provide linagliptin dosed as 2.5 mg twice daily (5 mg total daily dose) and a dose of metformin similar to the dose already being taken. When linagliptin plus metformin hydrochloride is used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycaemia (see section 4.4).

OR AS DIRECTED BY THE PHYSICIAN

Oral use

Linagliptin and Metformin hydrochloride Tablet should be administered with meal.

4.3 Contraindications

Renal impairment (e.g., serum creatinine levels at least 1.5 mg/dL [men] and at least 1.4 mg/dL [women]

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

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.

Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock.

Hepatic impairment, acute alcohol intoxication, alcoholism (see section 4.5).

4.4 Special warnings and precautions for use

General

LINO-M should not be used in patients with type 1 diabetes.

Hypoglycaemia

When linagliptin was added to a sulphonyl urea on a background of metformin, the incidence of hypoglycaemia was increased over that of placebo.

Sulphonyl ureas and insulin are known to cause hypoglycaemia. Therefore, caution is advised when LINO-M is used in combination with a sulphonyl urea and/or insulin. A dose reduction of the sulphonyl urea or insulin may be considered (see section 4.2).

Hypoglycaemia is not identified as adverse reaction for linagliptin, metformin, or linagliptin plus metformin. In clinical trials, the incidence rates of hypoglycaemia were comparably low in patients taking linagliptin in combination with metformin or metformin alone.

Lactic acidosis

Lactic acidosis, a very 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 diarrhoea or vomiting, 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 and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic impairment, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections 4.3 and 4.5).

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.

Administration of iodinated contrast agent

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.5.

Renal function

GFR should be assessed before treatment initiation and regularly thereafter, see section 4.2. Metformin is contraindicated in patients with GFR< 30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function, see section 4.3).

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal impairment. In patients with stable chronic heart failure, LINO-M may be used with a regular monitoring of cardiac and renal function.

For patients with acute and unstable heart failure, LINO-M is contraindicated (see section 4.3).

Surgery

Metformin 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.

Elderly

Caution should be exercised when treating patients 80 years and older (see section 4.2).

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

As LINO-M contains metformin, a patient with previously well controlled type 2 diabetes on LINO-M 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, LINO-M must be

stopped immediately and other appropriate corrective measures initiated.

Acute pancreatitis

Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Acute pancreatitis has been observed in patients taking linagliptin. In a cardiovascular and renal safety study (CARMELINA) with median observation period of 2.2 years, adjudicated acute pancreatitis was reported in 0.3% of patients treated with linagliptin and in 0.1% of patients treated with placebo. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, LINO-M should be discontinued; if acute pancreatitis is confirmed, LINO-M should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Bullous pemphigoid

Bullous pemphigoid has been observed in patients taking linagliptin. In the CARMELINA study, bullous pemphigoid was reported in 0.2% of patients on treatment with linagliptin and in no patient on placebo. If bullous pemphigoid is suspected, LINO-M should be discontinued.

Vitamin B12

Metformin may reduce vitamin B12 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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. However, such studies have been conducted with the individual active substances, i.e. linagliptin and metformin. Co-administration of multiple doses of linagliptin and metformin did not meaningfully alter the pharmacokinetics of either linagliptin or metformin in healthy volunteers and patients.

Linagliptin

In vitro assessment of interactions

Linagliptin is a weak competitive and a weak to moderate mechanism-based inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes. It is not an inducer of CYP isozymes.

Linagliptin is a P-glycoprotein substrate, and inhibits P-glycoprotein mediated transport of digoxin with low potency. Based on these results

and *in vivo* drug interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates.

In vivo assessment of interactions

Effects of other medicinal products on linagliptin

Clinical data described below suggest that the risk for clinically meaningful interactions by coadministered medicinal products is low.

Metformin:

Co-administration of multiple three-times-daily doses of 850 mg metformin hydrochloride with 10 mg linagliptin once daily did not clinical meaningfully alter the pharmacokinetics of linagliptin in healthy subjects.

Sulphonylureas:

The steady-state pharmacokinetics of 5 mg linagliptin were not changed by concomitant administration of a single 1.75 mg dose glibenclamide (glyburide).

Ritonavir:

Co-administration of a single 5 mg oral dose of linagliptin and multiple 200 mg oral doses of ritonavir, a potent inhibitor of P-glycoprotein and CYP3A4, increased the AUC and C_{max} of linagliptin approximately twofold and threefold, respectively. The unbound concentrations, which are usually less than 1% at the therapeutic dose of linagliptin, were increased 4-5-fold after co-administration with ritonavir. Simulations of

steady-state plasma concentrations of linagliptin with and without ritonavir indicated that the increase in exposure will not be associated with an increased accumulation. These changes in linagliptin pharmacokinetics were not considered to be clinically relevant. Therefore, clinically relevant interactions would not be expected with other P-glycoprotein/CYP3A4 inhibitors.

Rifampicin:

Multiple co-administration of 5 mg linagliptin with rifampicin, a potent inductor of P-glycoprotein and CYP3A4, resulted in a 39.6% and 43.8% decreased linagliptin steady-state AUC and C_{max} respectively, and about 30% decreased DPP-4 inhibition at trough. Thus full efficacy of linagliptin in combination with strong P-gp inducers might not be achieved, particularly if these are administered long-term. Co-administration with other potent inducers of P-glycoprotein and CYP3A4, such as carbamazepine, phenobarbital and phenytoin has not been studied.

Effects of linagliptin on other medicinal products

In clinical studies, as described below, linagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glyburide, simvastatin, warfarin, digoxin or oral contraceptives providing *in vivo* evidence of a low propensity for causing interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-glycoprotein, and organic cationic transporter (OCT).

Metformin:

Co-administration of multiple daily doses of 10 mg linagliptin with 850 mg metformin hydrochloride, an OCT substrate, had no relevant effect on the pharmacokinetics of metformin in healthy subjects. Therefore, linagliptin is not an inhibitor of OCT-mediated transport.

Sulphonylureas:

Co-administration of multiple oral doses of 5 mg linagliptin and a single oral dose of 1.75 mg glibenclamide (glyburide) resulted in clinically not relevant reduction of 14% of both AUC and C_{max} of glibenclamide. Because glibenclamide is primarily metabolised by CYP2C9, these data also support the conclusion that linagliptin is not a CYP2C9 inhibitor. Clinically meaningful interactions would not be expected with other sulphonylureas (e.g., glipizide, tolbutamide, and glimepiride) which, like glibenclamide, are primarily eliminated by CYP2C9.

Digoxin:

Co-administration of multiple daily doses of 5 mg linagliptin with multiple doses of 0.25 mg digoxin had no effect on the pharmacokinetics of digoxin in healthy subjects. Therefore, linagliptin is not an inhibitor of P-glycoprotein-mediated transport *in vivo*.

Warfarin:

Multiple daily doses of 5 mg linagliptin did not alter the pharmacokinetics of S(-) or R(+) warfarin, a CYP2C9 substrate, administered in a single dose.

Simvastatin:

Multiple daily doses of linagliptin had a minimal effect on the steady-state pharmacokinetics of simvastatin, a sensitive CYP3A4 substrate, in healthy subjects. Following administration of a supratherapeutic dose of 10 mg linagliptin concomitantly with 40 mg of simvastatin daily for 6 days, the plasma AUC of simvastatin was increased by 34%, and the plasma C_{max} by 10%.

Oral contraceptives:

Co-administration with 5 mg linagliptin did not alter the steady-state pharmacokinetics of levonorgestrel or ethinylestradiol.

Metformin

Combination requiring precautions for use

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.

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.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2. Co-administration of metformin with

• Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.

• Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.

• Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.

• Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are coadministered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of 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

4.6 Pregnancy and Lactation

The use of linagliptin has not been studied in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

A limited amount of data suggests that 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 reproductive toxicity (see section 5.3).

Non-clinical reproduction studies did not indicate an additive teratogenic effect attributed to the co-administration of linagliptin and metformin.

Linagliptin metformin combination should not be used during pregnancy. If the patient plans to become pregnant, or if pregnancy occurs, treatment with Linagliptin metformin combination should be discontinued and switched to insulin treatment as soon as possible in order to lower the risk of foetal malformations associated with abnormal blood glucose levels.

Breast-feeding

Studies in animals have shown excretion of both metformin and linagliptin into milk in lactating rats. Metformin is excreted in human

milk in small amounts. It is not known whether linagliptin is excreted into human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Linagliptin metformin combination therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effect of Linagliptin metformin combination on human fertility has not been studied. No adverse effects of linagliptin on fertility were observed in male or female rats (see section 5.3)

4.7 Effects on ability to drive and use machines

has no or negligible influence on the ability to drive and use machines. However, patients should be alerted to the risk of hypoglycaemia when Lino M is used in combination with other anti-diabetic medicinal products known to cause hypoglycaemia (e.g. sulphonyl ureas).

4.8 Undesirable effects

The safety of linagliptin 2.5 mg twice daily (or its bioequivalent of 5 mg once daily) in combination with metformin has been evaluated in over 6 800 patients with type 2 diabetes mellitus. In placebo-controlled studies, more than 1 800 patients were treated with the therapeutic dose of either 2.5 mg linagliptin twice daily (or its bioequivalent of 5 mg linagliptin once daily) in combination with metformin for ≥ 12/24 weeks.

In the pooled analysis of the seven placebo-controlled trials, the overall incidence of adverse events in patients treated with placebo and metformin was comparable to that seen with linagliptin 2.5 mg and metformin (54.3 and 49.0%). Discontinuation of therapy due to adverse events was comparable in patients who received placebo and metformin to patients treated with linagliptin and metformin (3.8% and 2.9%).

The most frequently reported adverse reaction for linagliptin plus metformin was diarrhoea (1.6%) with a comparable rate on metformin plus placebo (2.4%).

Hypoglycaemia may occur when linagliptin+metformin combination is administered together with sulphonylurea (≥ 1 case per 10 patients).

Tabulated list of adverse reactions

Adverse reactions reported in all clinical trials with the linagliptin+metformin combination or the use of the monocomponents (linagliptin or metformin) in clinical trials or from post-marketing experience are shown below according to system organ class. Adverse reactions previously reported with one of the individual active substances may be potential adverse reactions with linagliptin+metformin combination even if not observed in clinical trials with this medicinal product.

The adverse reactions are listed by system organ class and absolute frequency. 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), or very rare (< 1/10 000) and not known (cannot be estimated from the available data).

Table 2: Adverse reactions reported in patients who received linagliptin+metformin alone (as mono-components or in combination) or as add-on to other anti-diabetic therapies in clinical trial and from post-marketing experience

System organ class Adverse reaction	**Frequency of adverse reaction**
Infections and infestations	
Nasopharyngitis	uncommon
Immune system disorders	
Hypersensitivity (e.g. bronchial hyperreactivity)	uncommon
Metabolism and nutrition disorders	
Hypoglycaemia [1]	very common
Lactic acidosis [§]	very rare
Vitamin B12 decrease/deficiency [§, †]	common
Nervous system disorders	
Taste disturbance [§]	common
Respiratory, thoracic and mediastinal disorders	
Cough	uncommon

Gastrointestinal disorders	
Decreased appetite	uncommon
Diarrhoea	common
Nausea	common
Pancreatitis	rare #
Vomiting	uncommon
Constipation [2]	uncommon
Abdominal pain §	very common
Hepatobiliary disorders	
Liver function disorders [2]	uncommon
Hepatitis §	very rare
Skin and subcutaneous tissue disorders	
Angioedema	rare
Urticaria	rare
Erythema§	very rare
Rash	uncommon
Pruritus	uncommon
Bullous pemphigoid	rare #
Investigations	
Amylase increased	uncommon
Lipase increased*	common

* Based on lipase elevations > 3 × ULN observed in clinical trials

[#] Based on *Linagliptin cardiovascular and renal safety study (CARMELINA)*, see also below

[§] Identified adverse reactions of metformin monotherapy. Refer to Summary of Product Characteristics for metformin for additional information

[†] See section 4.4

[1] Adverse reaction observed in linagliptin+metformin combination with sulphonylurea

[2] Adverse reaction observed in linagliptin+metformin combination with insulin

Description of selected adverse reactions

Hypoglycaemia

In one study linagliptin was given as add-on to metformin plus sulphonylurea. When linagliptin and metformin were administered in combination with a sulphonylurea, hypoglycaemia was the most frequently reported adverse event (linagliptin plus metformin plus sulphonylurea 23.9% and 16.0% in placebo plus metformin plus sulphonylurea).

When linagliptin and metformin were administered in combination with insulin, hypoglycaemia was the most frequently reported adverse event, but occurred at comparable rate when placebo and metformin were combined with insulin (linagliptin plus metformin plus insulin 29.5% and

30.9% in the placebo plus metformin plus insulin group) with a low rate of severe (requiring assistance) episodes (1.5% and 0.9%).

Other adverse reactions

Gastrointestinal disorders such as, nausea, vomiting, diarrhoea and decreased appetite and abdominal pain occur most frequently during initiation of therapy with linagliptin metformin combination or metformin hydrochloride and resolve spontaneously in most cases. For prevention, it is recommended that linagliptin metformin combination be taken during or after meals. A slow increase in dose of metformin hydrochloride may also improve gastrointestinal tolerability.

Linagliptin cardiovascular and renal safety study (CARMELINA)

The CARMELINA study evaluated the cardiovascular and renal safety of linagliptin versus placebo in patients with type 2 diabetes and with increased CV risk evidenced by a history of established macrovascular or renal disease (see section 5.1). The study included 3 494 patients treated with linagliptin (5 mg) and 3 485 patients treated with placebo. Both treatments were added to standard of care targeting regional standards for HbA_{1c} and CV risk factors. The overall incidence of adverse events and serious adverse events in patients receiving linagliptin was similar to that in patients receiving placebo. Safety data from this study was in line with previous known safety profile of linagliptin.

In the treated population, severe hypoglycaemic events (requiring assistance) were reported in 3.0% of patients on linagliptin and in 3.1%

on placebo. Among patients who were using sulfonylurea at baseline, the incidence of severe hypoglycaemia was 2.0% in linagliptin-treated patients and 1.7% in placebo treated patients. Among patients who were using insulin at baseline, the incidence of severe hypoglycaemia was 4.4% in linagliptin-treated patients and 4.9% in placebo treated patients.

In the overall study observation period adjudicated acute pancreatitis was reported in 0.3% of patients treated with linagliptin and in 0.1% of patients treated with placebo.

In the CARMELINA study, bullous pemphigoid was reported in 0.2% of patients treated with linagliptin and in no patient treated with placebo.

Paediatric population

Overall, in clinical trials in paediatric patients with type 2 diabetes mellitus aged 10 to 17 years, the safety profile of linagliptin was similar to that observed in the adult population.

4.9 Overdose

Linagliptin

During controlled clinical trials in healthy subjects, single doses of up to 600 mg linagliptin (equivalent to 120 times the recommended dose) were not associated with a dose dependent increase in adverse events. There is no experience with doses above 600 mg in humans.

Metformin

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin hydrochloride or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin hydrochloride is haemodialysis.

Management

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, and institute clinical measures if required.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs.

ATC Code:
A10BD11

Lino-M combines two antihyperglycemic medicinal products with complementary mechanisms of action to improve glycaemic control in

patients with type 2 diabetes: linagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Mode of action

Linagliptin is an inhibitor of the enzyme DPP-4 (Dipeptidyl peptidase 4) an enzyme which is involved in the inactivation of the incretin hormones GLP-1 and GIP (glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide). These hormones are rapidly degraded by the enzyme DPP-4. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretins are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. Furthermore GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output. Linagliptin binds very effectively to DPP-4 in a reversible manner and thus leads to a sustained increase and a prolongation of active incretin levels. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion thus resulting in an overall improvement in the glucose homeostasis. Linagliptin binds selectively to DPP-4 and exhibits a >
10,000-fold selectivity versus DPP-8 or DPP-9
activity in vitro. Metformin

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

Metformin hydrochloride may act via

3 mechanisms:

(1) Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis,

(2) In muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation,

(3) and delay of intestinal glucose absorption

Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin hydrochloride increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.

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

5.2 Pharmacokinetic properties

Linagliptin

Absorption: The absolute bioavailability of linagliptin is approximately 30%. Co-administration of a high-fat meal with linagliptin prolonged the time to reach Cmax by 2 hours and lowered Cmax by 15%, but no influence on

AUC 0-72h was observed. No clinically relevant effect of Cmax and Tmax changes is expected; therefore linagliptin may be administered with or without food.

Distribution: As a result of tissue binding, the mean apparent volume of distribution at steady-state following a single 5 mg intravenous dose of linagliptin to healthy subjects is approximately 1110 litres, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent, decreasing from about 99% at 1 nmol/l to 75-89% at ≥ 30 nmol/l, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin At high concentrations, where DPP-4 is fully saturated, 70-80% of linagliptin was bound to other plasma proteins than DPP-4, hence 20-30% were unbound in plasma.

Biotransformation: Following a linagliptin oral 10 mg dose, approximately 5% of the radioactivity was excreted in urine. Metabolism plays a subordinate role in the elimination of linagliptin. One main metabolite with a relative exposure of 13.3% of linagliptin at steady-state was detected which was found to be pharmacologically inactive, and thus does not contribute to the plasma DPP-4 inhibitory activity of linagliptin.

Excretion: Following administration of an oral linagliptin dose to healthy subjects, approximately

85% of the administered radioactivity was eliminated in faeces (80%) or urine (5%) within 4 days of dosing. Renal clearance at steady-state was approximately 70 ml/min.

Metformin

Absorption: After an oral dose of metformin, Tmax is reached in 2.5 hours. Absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride 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 hydrochloride absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin hydrochloride absorption are non-linear.

At the recommended metformin hydrochloride doses and dosing schedules, steady-state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 microgram/ml. In controlled clinical trials, maximum metformin hydrochloride plasma levels (Cmax) did not exceed 5 microgram/ml, even at
maximum doses.

Food decreases the extent and slightly delays the absorption of metformin hydrochloride. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25%

decrease in AUC (area under the curve) and a 35-minute prolongation of the time to peak plasma concentration were observed. The clinical relevance of these decreases is unknown.

Distribution: Plasma protein binding is negligible. Metformin hydrochloride 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 volume of distribution (Vd) ranged between 63-276 l.

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

Excretion: Renal clearance of metformin hydrochloride is > 400 ml/min, indicating that metformin hydrochloride is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin hydrochloride in

5.3 Preclinical safety data

Linagliptin plus metformin

General toxicity studies in rats for up to 13 weeks were performed with the co-administration of linagliptin and metformin. The only observed

interaction between linagliptin and metformin was a reduction of body weight gain. No other additive toxicity caused by the combination of linagliptin and metformin was observed at AUC exposure levels up to 2- and 23-times human exposure, respectively.

An embryofetal development study in pregnant rats did not indicate a teratogenic effect attributed to the co-administration of linagliptin and metformin at AUC exposure levels up to 4- and 30-times human exposure, respectively.

Linagliptin

Liver, kidneys and gastrointestinal tract are the principal target organs of toxicity in mice and rats at repeat doses of linagliptin of more than 300 times the human exposure.

In rats, effects on reproductive organs, thyroid and the lymphoid organs were seen at more than
1500 times human exposure. Strong pseudo-allergic reactions were observed in dogs at medium doses, secondarily causing cardiovascular changes, which were considered dog-specific. Liver, kidneys, stomach, reproductive organs, thymus, spleen, and lymph nodes were target organs of toxicity in Cynomolgus monkeys at more than 450 times human exposure. At more than 100 times human exposure, irritation of the stomach was the major finding in these monkeys

6. Pharmaceutical Particulars

6.1 List of Excipients

Maize Starch L- Arginine

Copovidone

Colloidal Silicon Dioxide

Magnesium Stearate

Opadry II 85G53308 Orange

Opadry OY-B-28920 White

6.2 Incompatibilities

Not incompatibility is observed. This medicine should be swallowed whole with a drink of water,

do not crush or chew the tablets

6.3 Shelf-Life

24 Months

6.4 Special Precautions for storage

Store below 30°C. Protect from light and moisture.

6.5 Nature and Content of container

Alu- Alu Blister

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorization Holder

The ACME Laboratories Ltd.

Court de la ACME, ¼, Mirpur Road, Kallayanpur, Dhaka-1207

+88-02-8091051-3

export@acmeglobal.com (Business)

8. Marketing Authorization Number

CTD9219

9. Date of first authorization/renewal of the authorization

10/02/2023

10. Date of revision of the text

11/05/2025