For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

LINAXA M

WARNING: LACTIC ACIDOSIS

Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL. anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate. ratio; and metformin plasma levels generally >5 mcg/mL.

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.

Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information

If metformin-associated lactic acidosis is suspected, immediately discontinue Linagliptin And Metformin Hydrochloride and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

1. Generic Name

Linagliptin and Metformin Hydrochloride tablets 2.5 mg +500 mg, 2.5 mg+ 850 mg and 2.5 mg+1000 mg

2. Qualitative and quantitative composition

LINAXA M 2.5/ 500

Each film coated tablet contains:

Linagliptin.....2.5 mg

Metformin Hydrochloride I.P. ……. 500 mg

Excipients…….q.s.

Colours: Yellow oxide of Iron and Titanium dioxide I.P.

The Excipients used are Corn Starch, Povidone Meglumine (Kollidon 30 LP), Colloidal Silicon Dioxide, Magnesium Stearate, Novomix Yellow

LINAXA M 2.5/ 850

Each film coated tablet contains:

Linagliptin.....2.5 mg

Metformin Hydrochloride I.P. ……. 850 mg

Excipients…….q.s.

Colours: Red oxide of Iron, Yellow oxide of Iron and Titanium dioxide I.P.

The Excipients used are Corn Starch, Povidone (Kollidon 30 LP), Meglumine, Colloidal Silicon Dioxide, Magnesium Stearate, Novomix Light Brown

LINAXA M 2.5/ 1000

Each film coated tablet contains:

Linagliptin.....2.5 mg

Metformin Hydrochloride I.P. ……. 1000 mg

Excipients…….q.s.

Colours: Red oxide of Iron and Titanium dioxide I.P.

The Excipients used are Corn Starch, Povidone (Kollidon 30 LP), Meglumine, Colloidal Silicon Dioxide, Magnesium Stearate, Novomix Light Brown

3. Dosage form and strength

Dosage form: Film coated tablet

Strength: 2.5 mg +500 mg, 2.5 mg+ 850 mg and 2.5 mg+1000 mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated as an adjunct to diet and exercise to improve glycemia control in adults with type II Diabetes Mellitus when treatment with Linagliptin and Metformin is appropriate.

4.2 Posology and method of administration

Posology

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

The dose of antihyperglycaemic therapy with Linagliptin and Metformin Hydrochloride tablets should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability, while not exceeding the maximum recommended daily dose of 5 mg linagliptin plus 2,000 mg of metformin hydrochloride.

Patients inadequately controlled on maximal tolerated dose of metformin monotherapy

For patients not adequately controlled on metformin alone, the usual starting dose of Linagliptin and Metformin Hydrochloride tablets should provide linagliptin dosed as 2.5 mg twice daily (5 mg total daily dose) plus the dose of metformin already being taken.

Patients switching from co-administration of linagliptin and metformin

For patients switching from co-administration of linagliptin and metformin, Linagliptin and Metformin Hydrochloride tablets should be initiated at the dose of linagliptin and metformin already being taken.

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

The dose of Linagliptin and Metformin Hydrochloride tablets 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 sulphonylurea, a lower dose of the sulphonylurea may be required to reduce the risk of hypoglycaemia.

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

The dose of Linagliptin and Metformin Hydrochloride tablets 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.

For the different doses of metformin, Linagliptin and Metformin Hydrochloride tablets is available in strengths of 2.5 mg linagliptin plus 850 mg metformin hydrochloride and 2.5 mg linagliptin plus 1,000 mg metformin hydrochloride.

Special populations

Elderly

As metformin is excreted by the kidney, Linagliptin and Metformin Hydrochloride tablets 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.

Renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an 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.

Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin in patients with GFR<60 ml/min.

If no adequate strength of Linagliptin and Metformin Hydrochloride tablets is available, individual mono-components should be used instead of the fixed dose combination.

Hepatic impairment

LINAXA M is not recommended in patients with hepatic impairment due to the active substance metformin. Clinical experience with Linagliptin and Metformin Hydrochloride tablets in patients with hepatic impairment is lacking.

Paediatric population

The safety and efficacy of Linagliptin and Metformin Hydrochloride tablets in children and adolescents aged 0 to 18 years have not been established. No data are available.

Method of administration

As directed by the Physician.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed.

- 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.

4.4 Special warnings and precautions for use

General

Linagliptin and Metformin Hydrochloride tablets should not be used in patients with type 1 diabetes.

Hypoglycaemia

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

Sulphonylureas and insulin are known to cause hypoglycaemia. Therefore, caution is advised when Linagliptin and Metformin Hydrochloride tablets is used in combination with a sulphonylurea and/or insulin. A dose reduction of the sulphonylurea or insulin may be considered.

Hypoglycaemia is not identified as adverse reaction for linagliptin, metformin, or linagliptin plus metformin. In clinical trials, the incidence rates of hypoglycemia 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.

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnea, 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 reevaluated and found to be stable.

Renal function

GFR should be assessed before treatment initiation and regularly thereafter. Metformin is contraindicated in patients with GFR<30 ml/min and should be temporarily discontinued in the presence of conditions that alter renal function.

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal impairment. In patients with stable chronic heart failure, Linagliptin and Metformin Hydrochloride tablets may be used with a regular monitoring of cardiac and renal function.

For patients with acute and unstable heart failure, Linagliptin and Metformin Hydrochloride tablets is contraindicated.

Surgery

Metformin must be discontinued at the time of surgery under general, spinal or epidural anesthesia. 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.

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

As Linagliptin and Metformin Hydrochloride tablets contains metformin, a patient with previously well controlled type 2 diabetes on Linagliptin and Metformin Hydrochloride tablets 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, Linagliptin and Metformin Hydrochloride tablets 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 reported 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, Linagliptin and Metformin Hydrochloride tablets should be discontinued; if acute pancreatitis is confirmed, Linagliptin and Metformin Hydrochloride tablets 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 reported 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, Linagliptin and Metformin Hydrochloride tablets should be discontinued.

4.5 Drugs interactions

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 Cmax 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 Cmax 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 Cmax 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 Cmax 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.

Iodinated contrast agents

LINAXA M 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.

4.6 Pregnancy and lactation

Pregnancy

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.

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.

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

Linagliptin and Metformin Hydrochloride tablets should not be used during pregnancy. If the patient plans to become pregnant, or if pregnancy occurs, treatment with LINAXA M 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 and Metformin Hydrochloride tablets therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

A decrease in fertility linked to the pharmacological effects of the drug (prolactin-mediated effect) was observed in treated animals.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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 6800 patients with type 2 diabetes mellitus. In placebo-controlled studies, more than 1800 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 and Metformin Hydrochloride tablets 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 mono-components (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 LINAXA M, 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 B_{12} deficiency §	very rare
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 >3xULN observed in clinical trials

Based on reported Linagliptin cardiovascular and renal safety study (CARMELINA), see also below

§ Adverse reactions reported in patients who received metformin as monotherapy and that were not observed in patients receiving LINAXA M. Refer to Summary of Product Characteristics for metformin for additional information

1 Adverse reaction observed in combination of Linagliptin and Metformin Hydrochloride tablets with sulphonylurea

2 Adverse reaction observed in combination of Linagliptin and Metformin Hydrochloride tablets with insulin

Description of selected adverse reactions

Hypoglycaemia

In one reported 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 and Metformin Hydrochloride tablets or metformin hydrochloride and resolve spontaneously in most cases. For prevention, it is recommended that LINAXA M be taken during or after meals. A slow increase in dose of metformin hydrochloride may also improve gastrointestinal tolerability.

Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B12 deficiency (e.g. megaloblastic anaemia).

Linagliptin cardiovascular and renal safety reported study (CARMELINA)

The reported 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. The reported study included 3494 patients treated with linagliptin (5 mg) and 3485 patients treated with placebo. Both treatments were added to standard of care targeting regional standards for HbA1c 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 reported 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 reported 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 reported CARMELINA study, bullous pemphigoid was reported in 0.2% of patients treated with linagliptin and in no patient treated with placebo.

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 Mechanism of Action

Linagliptin:

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 glucosedependently 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 antihyperglycaemic 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 Pharmacodynamicproperties

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD1

Linagliptin and Metformin Hydrochloride tablets combines two antihyperglycaemic 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.

5.3 Pharmacokinetic properties

Bioequivalence studies in healthy subjects demonstrated that the Linagliptin and Metformin Hydrochloride tablets combination tablets are bioequivalent to co-administration of linagliptin and metformin hydrochloride as individual tablets.

Administration of Linagliptin and Metformin Hydrochloride tablets 2.5/1,000 mg with food resulted in no change in overall exposure of linagliptin. With metformin there was no change in AUC, however mean peak serum concentration of metformin was decreased by 18% when administered with food. A delayed time to peak serum concentrations by 2 hours was observed for metformin under fed conditions. These changes are not likely to be clinically meaningful.

The following statements reflect the pharmacokinetic properties of the individual active substances of Linagliptin and Metformin Hydrochloride tablets.

Linagliptin

The pharmacokinetics of linagliptin has been extensively characterised in healthy subjects and patients with type 2 diabetes. After oral administration of a 5 mg dose to healthy volunteers or patients, linagliptin was rapidly absorbed, with peak plasma concentrations (median Tmax) occurring 1.5 hours post-dose.

Plasma concentrations of linagliptin decline in a triphasic manner with a long terminal half-life (terminal half-life for linagliptin more than 100 hours), that is mostly related to the saturable, tight binding of linagliptin to DPP-4 and does not contribute to the accumulation of the active substance. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of 5 mg linagliptin, is approximately 12 hours. After once daily dosing of 5 mg linagliptin, steady-state plasma concentrations are reached by the third dose. Plasma AUC of linagliptin increased approximately 33% following 5 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for linagliptin AUC were small (12.6% and 28.5%, respectively). Due to the concentration dependent binding of linagliptin to DPP-IV, the pharmacokinetics of linagliptin based on total exposure is not linear; indeed total plasma AUC of linagliptin increased in a less than dose-proportional manner, while unbound AUC increases in a roughly dose-proportional manner. The pharmacokinetics of linagliptin was generally similar in healthy subjects and in patients with type 2 diabetes.

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 [14C] 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.

Elimination

Following administration of an oral [14C] 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.

Renal impairment

Under steady-state conditions, linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects. In moderate renal impairment, a moderate increase in exposure of about 1.7 fold was observed compared with control. Exposure in T2DM patients with severe RI was increased by about 1.4 fold compared to T2DM patients with normal renal function. Steady-state predictions for AUC of linagliptin in patients with ESRD indicated comparable exposure to that of patients with moderate or severe renal impairment. In addition, linagliptin is not expected to be eliminated to a therapeutically significant degree by hemodialysis or peritoneal dialysis. No dose adjustment of linagliptin is recommended in patients with renal impairment; therefore, linagliptin may be continued as a single entity tablet at the same total daily dose of 5 mg if Linagliptin and Metformin Hydrochloride tablets is discontinued due to evidence of renal impairment.

Hepatic impairment

In patients with mild moderate and severe hepatic impairment (according to the Child-Pugh classification), mean AUC and Cmax of linagliptin were similar to healthy matched controls following administration of multiple 5 mg doses of linagliptin.

Body Mass Index (BMI)

Body mass index had no clinically relevant effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. The clinical trials before marketing authorization have been performed up to a BMI equal to 40 kg/m^2.

Gender

Gender had no clinically relevant effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data.

Elderly

Age did not have a clinically relevant impact on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. Older subjects (65 to 80 years, oldest patient was 78 years) had comparable plasma concentrations of linagliptin compared to younger subjects. Linagliptin trough concentrations were also measured in elderly (age ≥ 70 years) with type 2 diabetes in a reported phase III study of 24 weeks duration. Linagliptin concentrations in this reported study were within the range of values previously observed in younger type 2

diabetes patients.

Paediatric population

A reported paediatric Phase 2 study examined the pharmacokinetics and pharmacodynamics of 1 mg and 5 mg linagliptin in children and adolescents ≥10 to <18 years of age with type 2 diabetes mellitus. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects. Linagliptin 5 mg showed superiority over 1 mg with regard to trough DPP-4 inhibition (72% vs 32%, p=0.0050) and a numerically larger reduction with regard to adjusted mean change from baseline in HbA1c (-0.63% vs -0.48%, n.s.). Due to the limited nature of the data set the results should be interpreted cautiously.

Race

Race had no obvious effect on the plasma concentrations of linagliptin based on a composite analysis of available pharmacokinetic data, including patients of Caucasian, Hispanic, African, and Asian origin. In addition the pharmacokinetic characteristics of linagliptin were found to be similar in dedicated phase I studies in Japanese, Chinese and Caucasian healthy subjects and African American type 2 diabetes patients.

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.

Elimination

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 plasma.*

Paediatric population

Reported Single dose study: after single doses of metformin hydrochloride 500 mg, paediatric patients have shown a similar pharmacokinetic profile to that observed in healthy adults.

Reported Multiple-dose study: data are restricted to one reported study. After repeated doses of 500 mg twice daily for 7 days in paediatric patients the peak plasma concentration (Cmax) and systemic exposure (AUC0-t) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

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.

A reported embryofetal development study in pregnant rats did not indicate a teratogenic effect attributed to the coadministration 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.

Linagliptin and its main metabolite did not show a genotoxic potential.

Oral 2 year carcinogenicity studies in rats and mice revealed no evidence of carcinogenicity in rats or male mice. A significantly higher incidence of malignant lymphomas only in female mice at the highest dose (> 200 times human exposure) is not considered relevant for humans (explanation: non-treatment related but due to highly variable background incidence). Based on these studies there is no concern for carcinogenicity in humans.

The NOAEL for fertility, early embryonic development and teratogenicity in rats was set at > 900

times the human exposure. The NOAEL for maternal-, embryo-fetal-, and offspring toxicity in rats was 49 times human exposure. No teratogenic effects were observed in rabbits at > 1,000 times human exposure. A NOAEL of 78 times human exposure was derived for embryo-fetal toxicity in rabbits, and for maternal toxicity the NOAEL was 2.1 times human exposure. Therefore, it is considered unlikely that linagliptin affects reproduction at therapeutic exposures in humans.

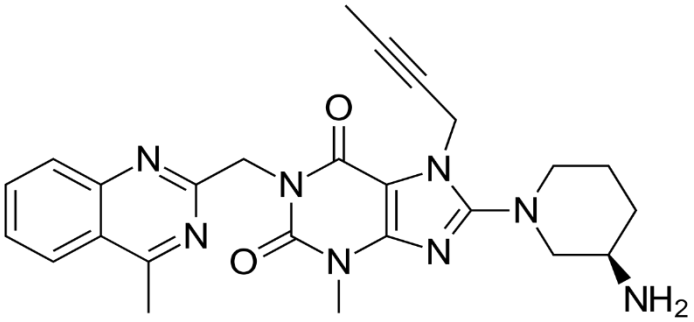
Metformin

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

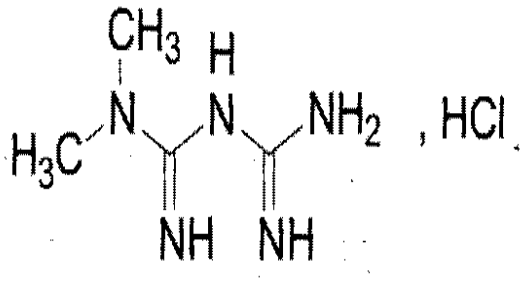
7. Description

Linagliptin:

Linagliptin is 8-[(3R)-3-Aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl) methyl]-3, 7-dihydro-1H-purine-2,6-dione. It has empirical formula of $C_{25}H_{28}N_8O_2$ and molecular weight of 472.54 g/mol. The chemical structure is as below:



Metformin Hydrochloride: Metformin Hydrochloride is 1, 1-dimethyl biguanide hydrochloride. having molecular formula of $C_4H_{11}N_5$, HCL and molecular weight is 165.6 the chemical structure is



Linagliptin and Metformin Hydrochloride tablets 2.5 mg +500 mg :

Light yellow, oval shaped, biconvex, film coated tablets, plain on both sides. The Excipients used are Corn Starch, Povidone (Kollidon 30 LP), Meglumine, Colloidal Silicon Dioxide, Magnesium Stearate, Novomix Yellow

Linagliptin and Metformin Hydrochloride tablets 2.5 mg+ 850 mg:

Light orange, oval shaped, biconvex, film coated tablets, plain on both sides. The Excipients used are Corn Starch, Povidone (Kollidon 30 LP), Meglumine, Colloidal Silicon Dioxide, Magnesium Stearate, Novomix Light Brown

Linagliptin and Metformin Hydrochloride tablets 2.5 mg+1000 mg :

Light pink, oval shaped , biconvex, film coated tablets, plain on both sides. The Excipients used are Corn Starch, Povidone (Kollidon 30 LP), Meglumine, Colloidal Silicon Dioxide, Magnesium Stearate, Novomix Light Brown

8. Pharmaceutical particulars

8.1 Incompatibilities

None known.

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

LINAXA M is available as Blister strip of 10 tablets.

8.4 Storage and handing instructions

Store at a temperature not exceeding 30^0 C.

Keep all medicines out of reach of children.

9. Patient Counselling Information

LINAXA M

Linagliptin and Metformin Hydrochloride tablets 2.5 mg +500 mg, 2.5 mg+ 850 mg and 2.5 mg+1000 mg

Read all of this leaflet carefully before you start taking this medicine because it contains Important information for you.

· Keep this leaflet. You may need to read it again.

· If you have any further questions, ask your doctor or pharmacist.

· This medicine has been prescribed for you only. Do not pass it on to others; it may harm Them, even if their signs of illness are the same as yours.

· If you get any side effects, talk to your doctor or pharmacist. This includes any possible side Effects not listed in this leaflet.

What is in this leaflet?

9.1 What LINAXA M is and what it is used for

Linaxa M contains Linagliptin and Metformin Hydrochloride tablets 2.5 mg +500 mg, 2.5 mg+ 850 mg and 2.5 mg+1000 mg

It is indicated as an adjunct to diet and exercise to improve glycemia control in adults with type II Diabetes Mellitus when treatment with Linagliptin and Metformin is appropriate.

9.2 What you need to know before you take LINAXA M

Do not take LINAXA M Tablets if:

- if you are allergic to linagliptin or metformin or any of the other ingredients of this medicine.
- if you have severely reduced kidney function.
- if you have uncontrolled diabetes, with, for example, severe hyperglycaemia (high blood glucose), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis or ketoacidosis. Ketoacidosis is a condition in which substances called ‘ketone bodies’ accumulate in the blood and which can lead to diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or your breath developing an unusual fruity smell.
- if you ever had a diabetic pre-coma.

- if you have a severe infection such as an infection affecting your lung or bronchial system or your kidney. Severe infections may lead to kidney problems, which can put you at risk for lactic acidosis.
- if you have lost a lot of water from your body (dehydration), e.g. due to long-lasting or severe diarrhoea, or if you have vomited several times in a row. Dehydration may lead to kidney problems, which can put you at risk for lactic acidosis.
- if you are treated for acute heart failure or have recently had a heart attack, have severe problems with your circulation (such as shock) or have breathing difficulties. This may lead to a lack in oxygen supply to tissue which can put you at risk for lactic acidosis.
- if you have liver problems.
- if you drink alcohol to excess, either every day or only from time to time.

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking LINAXA M.

Driving and using machines

LINAXA M has no or negligible influence on the ability to drive and use machines. However, taking LINAXA M in combination with medicines called sulphonylureas or with insulin can cause too low blood sugar level (hypoglycaemia), which may affect your ability to drive and use machines or work without safe foothold.

Warnings and precautions

Talk to your doctor or pharmacist before taking your medicine if:

• if you have type 1 diabetes (your body does not produce any insulin). LINAXA M should not be used to treat this condition.

• if you are taking insulin or an anti-diabetic medicine known as ‘sulphonylurea’, your doctor may want to reduce your dose of insulin or sulphonylurea when you take either of them together with LINAXA M in order to avoid low blood sugar (hypoglycaemia).

• if you have or have had a disease of the pancreas.

If you have symptoms of acute pancreatitis, like persistent, severe abdominal pain, you should consult your doctor.

If you encounter blistering of the skin it may be a sign for a condition called bullous pemphigoid. Your doctor may ask you to stop LINAXA M

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking LINAXA M

Risk of lactic acidosis.

Due to the metformin component, LINAXA M may cause a very rare, but very serious complication called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration, liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease). If any of the above apply to you, talk to your doctor for further instructions.

Stop taking LINAXA M for a short time if you have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instruction.

Stop taking LINAXA M and contact a doctor or the nearest hospital immediately if you experience some of the symptoms of lactic acidosis, as this condition may lead to coma.

Symptoms of lactic acidosis include:

• vomiting

• stomach ache (abdominal pain)

• muscle cramps

• a general feeling of not being well with severe tiredness

• difficulty in breathing

• reduced body temperature and heartbeat

Lactic acidosis is a medical emergency and must be treated in a hospital.

Other medicines and LINAXA M

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines including medicines obtained without a prescription.

In particular, do not take this medicine and tell your doctor if you are taking:

- Medicines which increase urine production (diuretics).
- Medicines used to treat pain and inflammation (NSAID and COX-2-inhibitors, such as ibuprofen and celecoxib).
- Certain medicines for the treatment of high blood pressure (ACE inhibitors and angiotensin II receptor antagonists).
- Medicines that may change the amount of metformin in your blood, especially if you have reduced kidney function (such as verapamil, rifampicin, cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole, crizotinib, olaparib).
- Carbamazepine, phenobarbital or phenytoin. These may be used to control fits (seizures) or chronic pain.
- Rifampicin this is an antibiotic used to treat infections such as tuberculosis.
- Medicines used to treat diseases that involve inflammation, like asthma and arthritis (corticosteroids).
- Bronchodilators (β-sympathomimetics) for the treatment of bronchial asthma.
- Alcohol-containing medicines.

LINAXA M with alcohol

Avoid excessive alcohol intake while taking LINAXA M since this may increase the risk of lactic acidosis.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

You should not use LINAXA M if you are pregnant. It is unknown if this medicine is harmful to the unborn child.

Metformin passes into human milk in small amounts. It is not known whether linagliptin passes into human milk. Talk to your doctor if you want to breast-feed while taking this medicine.

Driving and using machines

LINAXA M has no or negligible influence on the ability to drive and use machines.

However, taking LINAXA M in combination with medicines called sulphonylureas or with insulin can cause too low blood sugar level (hypoglycaemia), which may affect your ability to drive and use machines or work without safe foothold.

9.3 How to take LINAXA M Tablets

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

You should not exceed the maximum recommended daily dose of 5 mg linagliptin and 2,000 mg metformin hydrochloride.

If you take more LINAXA M than you should

If you take more LINAXA M tablets than you should have, you may experience lactic acidosis. Symptoms of lactic acidosis are non-specific such as feeling or being very sick, vomiting, stomach ache with muscle cramps, a general feeling of not being well with severe tiredness, and difficulty in breathing. Further symptoms are reduced body temperature and heartbeat. **If this happens to you, you may need immediate hospital treatment, as lactic acidosis can lead to coma. Stop taking this medicine immediately and contact a doctor or the nearest hospital straight away. Take the medicine pack with you**

If you forget to take LINAXA M

If you forget to take a dose, take it as soon as you remember it. However, if it is nearly time for the next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose. Never take two doses at the same time (morning or evening).

If you stop taking LINAXA M

Keep taking LINAXA M until your doctor tells you to stop. This is to help keep your blood sugar under control.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking LINAXA M and see a doctor or go to a hospital immediately if you notice any of the Following symptoms of low blood sugar (hypoglycaemia): trembling, sweating, anxiety, blurred vision, tingling lips, paleness, mood change, or confusion. Hypoglycaemia (frequency very common (may affect more than 1 in 10 people)) is an identified side effect for the combination of

LINAXA M plus sulphonylurea and for the combination LINAXA M plus insulin.

LINAXA M may cause a very rare (may affect up to 1 user in 10,000), but very serious side effect called lactic acidosis (see section 'Warnings and precautions'). If this happens you must stop taking LINAXA M and contact a doctor or the nearest hospital immediately, as lactic acidosis may lead to coma.

Some patients have experienced inflammation of the pancreas (pancreatitis; frequency rare, may affect up to 1 in 1000 people). Other side effects of LINAXA M include: Some patients have experienced allergic reactions (frequency rare), which may be serious, including wheezing and shortness of breath (bronchial hyperreactivity; frequency uncommon (may affect up to 1 in 100 people)). Some patients experienced rash (frequency uncommon), hives (urticaria; frequency rare), and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing (angioedema; frequency rare). If you experience any of the signs of illness mentioned above, stop taking LINAXA M and call your doctor right away. Your doctor may prescribe a medicine to treat your allergic reaction and a different medicine for your diabetes

Some patients have had the following side effects while taking LINAXA M:

• Common (may affect up to 1 in 10 people): diarrhoea, blood enzyme increase (lipase increase), feeling sick (nausea)

• Uncommon: inflamed nose or throat (nasopharyngitis), cough, loss of appetite (decreased appetite), being sick (vomiting), blood enzyme increase (amylase increase), itching (pruritus)

• Rare: blistering of skin (bullous pemphigoid)

Some patients have experienced the following side effects while taking LINAXA M with insulin

• Uncommon: liver function disorders, constipation

Side effects when taking metformin alone, that were not described for LINAXA M:

• Very common: abdominal pain.

• Common (may affect up to 1 in 10 people): a metallic taste (taste disturbance).

• Very rare (may affect up to 1 in 10,000 people): decreased vitamin B12 levels, hepatitis (a problem with your liver), skin reaction as redness of the skin (erythema).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store LINAXA M Tablets.

Store at a temperature not exceeding 30ºC.

Keep the medicines out of reach of children.

9.6 Content of the pack and other information

LINAXA M contain active substances Linagliptin and Metformin Hydrochloride

LINAXA M is available as Blister strip of 10 tablets.

Linagliptin and Metformin Hydrochloride tablets 2.5 mg +500 mg :

The Excipients used are Corn Starch, Povidone (Kollidon 30 LP), Meglumine, Colloidal Silicon Dioxide, Magnesium Stearate, Novomix Yellow

Linagliptin and Metformin Hydrochloride tablets 2.5 mg+ 850 mg:

The Excipients used are Corn Starch, Povidone (Kollidon 30 LP), Meglumine, Colloidal Silicon Dioxide, Magnesium Stearate, Novomix Light Brown

Linagliptin and Metformin Hydrochloride tablets 2.5 mg+1000 mg :

The Excipients used are Corn Starch, Povidone (Kollidon 30 LP), Meglumine, Colloidal Silicon Dioxide, Magnesium Stearate, Novomix Light Brown

10. Details of manufacturer

TORRENT PHARMACEUTICALS LTD.

32 No. Middle camp, NH-10,

East District, Gangtok, Sikkim-737 135.

11. Details of permission or licence number with date

M/563/2010 issued on 24/05/2022

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/LINAXA M 2.5 mg/500 mg, 850 mg, 1000 mg/Apr-23/01/PI