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

LINAXA M XR

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 Linaxa M XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

1. Generic Name

Linagliptin And Metformin Hydrochloride Extended Release Tablets

2. Qualitative and quantitative composition

<u>Linaxa M XR Extended Release Tablets 5 mg +1000 mg</u>

Each film coated tablet contains:

Linagliptin ……..... 5 mg

Metformin Hydrochloride I.P. ..... 1000 mg

(In Extended Release form)

Excipients …… q.s.

Colours: Titanium Dioxide I.P.

The excipients used are Microcrystalline Cellulose (Avicel PH 101), Povidone Sodium CMC–8M30, Purified Water, Isopropyl Alcohol, Hypromellose, Magnesium Stearate, Talc, Hydroxy Propyl Methyl Cellulose, Methylene Chloride, Meglumine, Polyethylene glycol 6000, Opadry Complete FCS 02H580032 White

3. Dosage form and strength

Dosage form: film coated Tablets

Strength: 5 mg+ 1000 mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients with type-II diabetes mellitus when treatment with Linagliptin and Metformin is appropriate.

4.2 Posology and method of administration

Posology

The dosage Linaxa M XR should be individualized on the basis of both effectiveness and tolerability, while not exceeding the maximum recommended total daily dose of linagliptin 5 mg and metformin hydrochloride (HCl) 2000 mg. Linaxa M XR should be given once daily with a meal.

Recommended starting dose:

- In patients currently not treated with metformin, initiate Linaxa M XR treatment with 5 mg linagliptin/1000 mg metformin HCl extended-release once daily with a meal.
- In patients already treated with metformin, Linaxa M XR with 5 mg of linagliptin total daily dose and a similar total daily dose of metformin HCl once daily with a meal.
- In patients already treated with linagliptin and metformin switch to Linaxa M XR containing 5 mg of linagliptin total daily dose and a similar total daily dose of metformin HCl once daily with a meal.

Linaxa M XR should be swallowed whole. The tablets must not be split, crushed, dissolved, or chewed.

Linaxa M XR 5 mg linagliptin/1000 mg metformin HCl extended-release tablet should be taken as a single tablet once daily. Patients using 5 mg linagliptin/1000 mg metformin HCl extended-release tablets should take two tablets together once daily.

Recommended Dosing in Renal Impairment

Assess renal function prior to initiation Linaxa M XR and periodically thereafter.

Linaxa M XR) is contraindicated in patients with an estimated glomerular filtration rate

(eGFR) below 30 mL/min/1.73 m^2

Initiation Linaxa M XR in patients with an eGFR between 30-45 mL/min/1.73 m^2 is not recommended.

In patients taking Linaxa M XR whose eGFR later falls below 45 mL/min/1.73 m^2 assess benefit/risk of continuing therapy.

Discontinue Linaxa M XR if the patient's eGFR later falls below 30 mL/min/1.73 m^2

Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue Linaxa M XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m ; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart Linaxa M XR if renal function is stable.

Method of administration

As directed by the Physician.

4.3 Contraindications

- Severe renal impairment (eGFR below 30 mL/min/1.73 m).
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis.
- Hypersensitivity to linagliptin, metformin, or any of the excipients in Linaxa M XR, reactions such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity have occurred with linagliptin.

4.4 Special warnings and precautions for use

Lactic Acidosis

Metformin

There have been post marketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgia's, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant Brady arrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation Linagliptin And Metformin Hydrochloride treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue Linagliptin And Metformin Hydrochloride and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment: The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include

- Before initiating Linagliptin And Metformin Hydrochloride, obtain an estimated glomerular filtration rate (eGFR).
- Linagliptin And Metformin Hydrochloride is contraindicated in patients with an eGFR less than 30 mL/min/1.732 m.

- Initiation Linagliptin And Metformin Hydrochloride is not recommended in patients with eGFR between 30 – 45 mL/min/1.73 m2.
- Obtain an eGFR at least annually in all patients taking Linagliptin And Metformin Hydrochloride. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
- In patients taking Linagliptin And Metformin Hydrochloride whose eGFR later falls below 45 mL/min/1.73 m2, assess the benefit and risk of continuing therapy.

Drug Interactions: The concomitant use Linagliptin And Metformin Hydrochloride with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation. Therefore, consider more frequent monitoring of patients.

Age 65 or Greater: The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.

Radiological Studies with Contrast: Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop Linagliptin And Metformin Hydrochloride at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m ; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Reevaluate eGFR 48 hours after the imaging procedure, and restart Linaxa M XR if renal function is stable.

Surgery and Other Procedures: Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. Linaxa M XR should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States: Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue Linaxa M XR.

Excessive Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving Linagliptin And Metformin Hydrochloride.

Hepatic Impairment: Patients with hepatic impairment have developed cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use Linagliptin And Metformin Hydrochloride in patients with clinical or laboratory evidence of hepatic disease.

Pancreatitis

Acute pancreatitis, including fatal pancreatitis, has been reported in patients treated with linagliptin. In reported clinical trial, acute pancreatitis was reported in 9 (0.3%) patients treated with linagliptin and in 5 (0.1%) patients treated with placebo. Two patients treated with linagliptin in reported clinical trial had acute pancreatitis with a fatal outcome. There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients treated with

linagliptin.

Take careful notice of potential signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue Linaxa M XR and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Linagliptin And Metformin Hydrochloride.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin secretagogues and insulin are known to cause hypoglycemia. The use linagliptin in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin was associated with a higher rate of hypoglycemia compared with placebo in reported study. Metformin may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with Linagliptin And Metformin Hydrochloride.

Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with linagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred predominantly within the first 3 months after initiation of treatment with linagliptin, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue Linagliptin And Metformin Hydrochloride, assess for other potential causes for the event, and institute alternative treatment for diabetes.

Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema to another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with Linagliptin And Metformin Hydrochloride.

Vitamin B Deficiency

In metformin, reported study of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B levels was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to interference with B absorption from the B -intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B supplementation. Certain individuals (those with inadequate vitamin B or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B levels. Measure hematologic parameters on an annual basis and vitamin B at 2 to 3 year intervals in patients on Linagliptin And Metformin Hydrochlorideand manage any abnormalities.

Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

Bullous Pemphigoid

Bullous pemphigoid was reported in 7 (0.2%) patients treated with linagliptin compared to none in patients treated with placebo in the reported clinical trial and 3 of these patients were

hospitalized due to bullous pemphigoid. Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving Linaxa M XR. If bullous pemphigoid is suspected, Linagliptin And Metformin Hydrochlorideshould be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Heart Failure

An association between DPP-4 inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

Consider the risks and benefits Linagliptin And Metformin Hydrochlorideprior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation Linagliptin And Metformin Hydrochloride.

4.5 Drugs interactions

Table 1 Clinically Relevant Interactions with Linagliptin And Metformin Hydrochloride

Carbonic Anhydrase Inhibitors	
Clinical Impact	Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis
Intervention	Concomitant use of these drugs with Linagliptin And Metformin Hydrochloride Linagliptin And Metformin Hydrochloride may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients.
Drugs that Reduce Metformin Clearance	
Clinical Impact	Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis

Intervention	Consider the benefits and risks of concomitant use.
Alcohol	
Clinical Impact	Alcohol is known to potentiate the effect of metformin on lactate metabolism. Intervention Warn patients against excessive alcohol intake while receiving Linagliptin And Metformin Hydrochloride
Insulin or Insulin Secretagogues	
Clinical Impact	The use of linagliptin in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin was associated with a higher rate of hypoglycemia compared with placebo in reported clinical trials. Metformin may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue.
Intervention	Coadministration Linagliptin And Metformin Hydrochloride with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
Drugs Affecting Glycemic Control	
Clinical Impact	Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid.
Intervention	When such drugs are administered to a patient receiving Linagliptin And Metformin Hydrochloride, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving Linagliptin And Metformin Hydrochloride the patient should be observed closely for hypoglycemia.

Inducers of P-glycoprotein or CYP3A4 Enzymes	
Clinical Impact	Rifampin decreased linagliptin exposure, suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-gp or CYP3A4 inducer.
Intervention	Use of alternative treatments is strongly recommended when linagliptin is to be administered with a strong P-gp or CYP3A4 inducer.

4.6 Use in specific population (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy and laction

Pregnancy

The limited data with Linagliptin And Metformin Hydrochlorideand linagliptin use in pregnant women are not sufficient to inform a Linagliptin And Metformin Hydrochloride-associated or linagliptin-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy.

In animal reproduction studies, no adverse developmental effects were observed when the combination of linagliptin and metformin was administered to pregnant rats during the period of organogenesis at doses similar to the maximum recommended clinical dose, based on exposure.

The estimated background risk of major birth defects is 6% to 10% in women with pre-gestational diabetes with a HbA1c>7 and has been reported to be as high as 20% to 25% in women with HbA1c>10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Human Data

Published data from postmarketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and

inconsistent comparator groups.

Animal Data

Linagliptin and metformin, the components Linagliptin And Metformin Hydrochloride, were coadministered to pregnant Wistar Han rats during the period of organogenesis. No adverse developmental outcome was observed at doses similar to the maximum recommended clinical dose, based on exposure. At higher doses associated with maternal toxicity, the metformin component of the combination was associated with an increased incidence of fetal rib and scapula malformations at ≥9-times a 2000 mg clinical dose, based on exposure.

Linagliptin

No adverse developmental outcome was observed when linagliptin was administered to pregnant Wistar Han rats and Himalayan rabbits during the period of organogenesis at doses up to 240 mg/kg/day and 150 mg/kg/day, respectively. These doses represent approximately 943-times (rats) and 1943-times (rabbits) the 5 mg clinical dose, based on exposure. No adverse functional, behavioral, or reproductive outcome was observed in offspring following administration of linagliptin to Wistar Han rats from gestation day 6 to lactation day 21 at a dose 49-times the 5 mg clinical dose, based on exposure. Linagliptin crosses the placenta into the fetus following oral dosing in pregnant rats and rabbits.

Metformin Hydrochloride

Metformin hydrochloride did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits at up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of approximately 2 and 6-times a clinical dose of 2000 mg, based on body surface area (mg/m) for rats and rabbits, respectively.

Lactation

There is no information regarding the presence Linagliptin And Metformin Hydrochlorideor linagliptin in human milk, the effects on the breastfed infant, or the effects on milk production. However, linagliptin is present in rat milk. Limited published studies report that metformin is present in human milk However, there is insufficient information to determine the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Linagliptin And Metformin Hydrochlorideand any potential adverse effects on the breastfed child from Linaxa M XR or from the underlying maternal condition.

Data

Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

Pediatric Use

Safety and effectiveness Linagliptin And Metformin Hydrochloridehave not been established in pediatric patients.

Geriatric Use

Linagliptin is minimally excreted by the kidney; however, metformin is substantially excreted by the kidney

Linagliptin

In the 15 type 2 diabetes studies with linagliptin, 1085 linagliptin-treated patients were 65 years of age and older (including 131 linagliptin-treated patients 75 years of age and older). Of these 15 studies, 12 were double-blind placebo-controlled. In these 12 studies, 591 linagliptin-treated patients were 65 years of age and older (including 82 linagliptin-treated patients 75 years of age and older). In these linagliptin studies, no overall differences in safety or effectiveness of linagliptin were observed between geriatric patients and younger adult patients.

Metformin

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients.

Renal Impairment

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Linaxa M XR is contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m.

If Linaxa M XR is discontinued due to evidence of renal impairment, linagliptin may be continued as a single entity tablet at the same total daily dose of 5 mg. No dose adjustment of linagliptin is recommended in patients with renal impairment. In the linagliptin treatment arm of the reported trial (63%) patients had renal impairment (eGFR <60 mL/min/1.73m). Approximately 20% of the population had eGFR ≥45 to <60 mL/min/1.73 m, 28% of the population had eGFR ≥30 to <45 mL/min/1.73 m and 15% had eGFR <30 mL/min/1.73 m . The overall incidence of adverse reactions were generally similar between the linagliptin and placebo treatment arms.

Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis Linagliptin And Metformin Hydrochloride is not recommended in patients with hepatic impairment.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Lactic Acidosis [see Warnings and Precautions (4.3)]
- Pancreatitis [see Warnings and Precautions (4.3)]
- Use with Medications Known to Cause Hypoglycemia [see Warnings and Precautions (4.3)]
- Hypersensitivity Reactions [see Warnings and Precautions (4.3)]
- Vitamin B Deficiency [see Warnings and Precautions (4.3)]
- Severe and Disabling Arthralgia [see Warnings and Precautions (4.3)]
- Bullous Pemphigoid [see Warnings and Precautions (4.3)]

4.9 Overdose

In the event of an overdose with Linagliptin And Metformin Hydrochloride, contact the Poison Control Center. Removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely. However, metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful partly for removal of accumulated metformin from patients in whom Linagliptin And Metformin Hydrochloride overdosage is suspected.

Metformin

Overdose of metformin has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin.

5. Pharmacological properties

5.1 Mechanism of Action

Linagliptin:

Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Thus, linagliptin increases the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretin hormones 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.

Metformin:

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin

response may actually decrease.

5.2 Pharmacodynamic properties

Linagliptin

Linagliptin binds to DPP-4 in a reversible manner and increases the concentrations of incretin hormones. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion, thus resulting in a better regulation of the glucose homeostasis. Linagliptin binds selectively to DPP-4 and selectively inhibits DPP-4, but not DPP-8 or DPP-9 activity in vitro at concentrations approximating therapeutic exposures.

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, 4-way crossover study, 36 healthy subjects were administered a single oral dose of linagliptin 5 mg, linagliptin 100 mg (20 times the recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either the recommended dose of 5 mg or the 100-mg dose. At the 100-mg dose, peak linagliptin plasma concentrations were approximately 38-fold higher than the peak concentrations following a 5-mg dose.

5.3 Pharmacokinetic properties

Administration Linaxa M XR with a high-fat meal resulted in up to 7% to 22% decrease in overall exposure (AUC) of linagliptin; this effect is not clinically relevant. For metformin extended-release, high-fat meals increased systemic exposure (AUC) 0-72 0-tz by approximately 54% to 71% relative to fasting, while C is increased up to 11%. Meals prolonged T by approximately 3 hours.

Absorption

Linagliptin:

The absolute bioavailability of linagliptin is approximately 30%. Following oral administration, plasma concentrations of linagliptin decline in at least a biphasic manner with a long terminal half-life (>100 hours), related to the saturable binding of linagliptin to DPP-4. However, the prolonged elimination does not contribute to the accumulation of the drug. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of linagliptin 5 mg, is approximately 12 hours. After once-daily dosing, steady-state plasma concentrations of linagliptin 5 mg are reached by the third dose, and C and AUC increased by a factor of 1.3 at steady-state compared with the first dose. Plasma AUC of linagliptin increased in a less than doseproportional manner in the dose range of 1 to 10 mg. The pharmacokinetics of linagliptin is similar in healthy subjects and in patients with type 2 diabetes.

Metformin

Following a single oral dose of 1000 mg (2 × 500 mg tablets) metformin extended release after a meal, the time to reach maximum plasma metformin concentration (T_{max}) is achieved at approximately 7 to 8 hours. In both single- and multiple-dose studies in healthy subjects, once daily 1000 mg (2 × 500 mg tablets) dosing provides equivalent systemic exposure, as measured by AUC, and up to 35% higher C_{max} of metformin relative to the immediate-release given as 500 mg twice daily.

Single oral doses of metformin extended-release from 500 mg to 2500 mg resulted in less than

proportional increase in both AUC and C_{max}. Low-fat and high-fat meals increased the systemic exposure (as measured by AUC) from metformin extended release tablets by about 38% and 73%, respectively, relative to fasting. Both meals prolonged metformin T_{max} by approximately 3 hours but C_{max} was not affected.

Distribution

Linagliptin

The mean apparent volume of distribution at steady-state following a single intravenous dose of linagliptin 5 mg to healthy subjects is approximately 1110 L, 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% to 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% to 80% of linagliptin remains bound to plasma proteins and 20% to 30% is unbound in plasma. Plasma binding is not altered in patients with renal or hepatic impairment.

Metformin

The apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin hydrochloride tablets 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time.

Elimination

Linagliptin

Linagliptin has a terminal half-life of about 200 hours at steady-state, though the accumulation half-life is about 11 hours. Renal clearance at steady-state was approximately 70 mL/min.

Metformin:

Metformin has a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Metabolism

Linagliptin:

Following oral administration, the majority (about 90%) of linagliptin is excreted unchanged, indicating that metabolism represents a minor elimination pathway. A small fraction of absorbed linagliptin is metabolized to a pharmacologically inactive metabolite, which shows a steady-state exposure of 13.3% relative to linagliptin.

Metformin:

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

Excretion

Linagliptin:

Following administration of an oral [$_{14}$C] linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated via the enterohepatic system (80%) or urine (5%)

within 4 days of dosing.

Metformin:

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

No carcinogenicity, mutagenicity, or impairment of fertility studies have been conducted with the combination of linagliptin and metformin HCl.

Linagliptin

Linagliptin did not increase the incidence of tumors in male and female rats in a 2-year study at doses of 6, 18, and 60 mg/kg. The highest dose of 60 mg/kg is approximately 418 times the clinical dose of 5 mg/day based on AUC exposure. Linagliptin did not increase the incidence of tumors in mice in a 2-year study at doses up to 80 mg/kg (males) and 25 mg/kg (females), or approximately 35 and 270 times the clinical dose based on AUC exposure. Higher doses of linagliptin in female mice (80 mg/kg) increased the incidence of lymphoma at approximately 215 times the clinical dose based on AUC exposure.

Linagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a chromosomal aberration test in human lymphocytes, and an in vivo micronucleus assay.

In fertility studies in rats, linagliptin had no adverse effects on early embryonic development, mating, fertility, or bearing live young up to the highest dose of 240 mg/kg (approximately 943 times the clinical dose based on AUC exposure).

Metformin Hydrochloride

Long-term carcinogenicity studies have been performed in Sprague Dawley rats at doses of 150, 300, and 450 mg/kg/day in males and 150, 450, 900, and 1200 mg/kg/day in females. These doses are approximately 2, 4, and 8 times in males, and 3, 7, 12, and 16 times in females of the maximum recommended human daily dose of 2000 mg/kg/day based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female rats. A carcinogenicity study was also performed in Tg.AC transgenic mice at doses of up to 2000 mg/kg/day applied dermally. No evidence of carcinogenicity was observed in male or female mice.

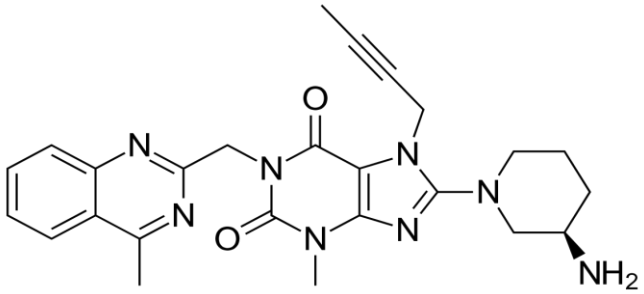
Genotoxicity assessments in the Ames test, gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes) and in vivo mouse micronucleus tests were negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 2 times the MRHD based on body surface area comparisons.

7. Description

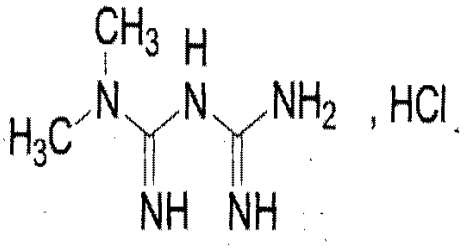
Linagliptin:

Linagliptin is 8-[(3R)-3-Aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methyl quinazolin-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 g/mol. the chemical structure is



<u>Linaxa M XR Extended Release Tablets 5 mg +1000 mg</u>

White to off-white coloured, biconvex, oval shaped, film coated tablets, plain on both sides. The excipients used are Microcrystalline Cellulose (Avicel PH 101), Povidone Sodium CMC–8M30, Purified Water, Isopropyl Alcohol, Hypromellose, Magnesium Stearate, Talc, Hydroxy Propyl Methyl Cellulose, Methylene Chloride, Meglumine, Polyethylene glycol 6000, Opadry Complete FCS 02H580032 White

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 XR Tablets is available in blisters strips of 10 Tablets each.

8.4 Storage and handing instructions

Store at a Temperature Not Exceeding 25°C, Protected From Moisture.

Keep out of reach of children.

9. Patient Counselling Information

Linaxa M XR

(Linagliptin And Metformin Hydrochloride Extended Release Tablets, 5mg+ 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 XR is and what it is used for

Linaxa M XR contains Linagliptin And Metformin Hydrochloride Extended Release Tablets 5mg+ 1000 mg.

It is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients 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 XR

Do not take Linaxa M XR Tablets if you:

- Have or have had inflammation of your pancreas (pancreatitis)..
- Have kidney problems.
- have liver problem
- have heart problems, including congestive heart failure
- are 65 years of age or older.
- drink alcohol very often, or drink a lot of alcohol in short term ("binge" drinking).
- are going to get an injection of dye or contrast agents for an x-ray procedure.
- have type 1 diabetes. Linaxa M XR should not be used to treat people with type 1 diabetes.

- have low levels of vitamin B_{12} in your blood.
- are pregnant or plan to become pregnant. It is not known if Linaxa M XR will harm your unborn baby. If you are pregnant, talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. Linaxa M XR may pass into your breast milk and may harm your baby. Talk with your healthcare provider about the best way to feed your baby if you take Linaxa M XR.
- are a woman who has not gone through menopause (premenopausal) who does not have periods regularly or at all. Linaxa M XR can cause the release of an egg from an ovary in a woman (ovulation). This can increase your chance of getting pregnant. Tell your healthcare provider right away if you become pregnant while taking Linaxa M XR

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 XR.

Warnings and precautions

Lactic Acidosis

Metformin

There have been postmarketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation Linaxa M XR. In Linaxa M XR-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue Linaxa M XR and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment: The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the

patient's renal function include

- Before initiating Linaxa M XR, obtain an estimated glomerular filtration rate (eGFR).
- Linaxa M XR is contraindicated in patients with an eGFR less than 30 mL/min/1.73^2 m.
- Initiation Linaxa M XR is not recommended in patients with eGFR between 30 – 45 mL/min/1.73 m^2.
- Obtain an eGFR at least annually in all patients taking Linaxa M XR. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
- In patients taking Linaxa M XR whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit and risk of continuing therapy.

Pancreatitis

Acute pancreatitis, including fatal pancreatitis, has been reported in patients treated with linagliptin. In the reported clinical trial, acute pancreatitis was reported in 9 (0.3%) patients treated with linagliptin and in 5 (0.1%) patients treated with placebo. Two patients treated with linagliptin in the reported clinical trial had acute pancreatitis with a fatal outcome. There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients treated with linagliptin.

Take careful notice of potential signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue Linaxa M XR and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the

Development of pancreatitis while using Linaxa M XR

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin secretagogues and insulin are known to cause hypoglycemia. The use of linagliptin in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin was associated with a higher rate of hypoglycemia compared with placebo in reported clinical trials. Metformin may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with Linaxa M XR

Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with linagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred predominantly within the first 3 months after initiation of treatment with linagliptin, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue Linaxa M XR, assess for other potential causes for the event, and institute alternative treatment for diabetes.

Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema to another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with Linaxa M XR.

Vitamin B Deficiency

In metformin reported clinical trials of 29-week duration, a decrease to subnormal levels of

previously normal serum vitamin B levels was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to interference with B absorption from the B - intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B supplementation. Certain individuals (those with inadequate vitamin B or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B levels. Measure hematologic parameters on an annual basis and vitamin B at 2 to 3 year intervals in patients on Linaxa M XR and manage any abnormalities.

Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

Bullous Pemphigoid

Bullous pemphigoid was reported in 7 (0.2%) patients treated with linagliptin compared to none in patients treated with placebo in the reported clinical trial, and 3 of these patients were hospitalized due to bullous pemphigoid. Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving Linaxa M XR. If bullous pemphigoid is suspected, Linaxa M XR should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Heart Failure

An association between DPP-4 inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. Consider the risks and benefits Linaxa M XR prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation Linaxa M XR

Stop taking Linaxa M XR 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 XR 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 XR

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:

- insulin or other medicines that can lower your blood sugar
- diuretics (water pills)
- rifampin (Rifadin, Rimactane, Rifater, Rifamate), an antibiotic that is used to treat tuberculosis

Linaxa M XR with alcohol

Avoid excessive alcohol intake while taking Linaxa M XR 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 XR 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.

9.3 How to take Linaxa M XR 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 linagliptin metformin hydrochloride Extended Release Tablets.

If you take more Linaxa M XR than you should

If you take more Linaxa M XR 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 XR

If you miss a dose, take it with food as soon as you remember. If you do not remember until it is

time for your next dose, skip the missed dose and go back to your regular schedule. Do not take 2 doses Linaxa M XR at the same time.

If you stop taking Linaxa M XR

Keep taking Linaxa M XR 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 XR and see a doctor or go to a hospital immediately

Lactic acidosis. Metformin hydrochloride, one of the medicines Linaxa M XR, can cause a rare but serious condition called lactic acidosis (a build-up of lactic acid in the blood) that can cause death.

Lactic acidosis is a medical emergency and must be treated in a hospital. Stop taking Linaxa M XR and call your healthcare provider right away or go to the nearest hospital emergency room if you get any of the following symptoms of lactic acidosis:

Feel very weak and tired

- Have unusual (not normal) Muscle pain
- Have trouble breathing
- Have unexplained stomach or Intestinal problems with Nausea and vomiting, or Diarrhea
- Have unusual sleepiness or sleep longer than Usual
- Feel cold, especially in your arms and legs
- Feel dizzy or lightheaded
- Have a slow or irregular heartbeat

You have a higher chance of getting lactic acidosis with Linaxa M XR **if you:**

- Have severe kidney problems.
- Have liver problems.
- Drink a lot of alcohol (very often or short-term "binge" drinking).
- Get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids.
- Have certain x-ray tests with injectable dyes or contrast agents.
- Have surgery or other procedures for which you need to restrict the amount of food and liquid you eat and drink.
- Have congestive heart failure.
- Have a heart attack, severe infection, or stroke.
- Are 65 years of age or older.

Inflammation of the pancreas (pancreatitis) which may be severe and lead to

- Death. Certain medical problems make you more likely to get pancreatitis.

Before you start taking Linaxa M XR tell your healthcare provider if you have ever had:

- Inflammation of your pancreas (pancreatitis)
- A history of alcoholism
- Stones in your gallbladder (gallstones)
- High blood triglyceride levels

Stop taking Linaxa M XR and call your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

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

9.5 How to store Linaxa M XR Tablets.

Store at a Temperature Not Exceeding 25°C, Protected From Moisture.

Keep out of reach of children.

9.6 Content of the pack and other information

Linaxa M XR contain active substances Linaxa M XR Extended Release Tablets

Linaxa M XR is available in blisters strips of 10 Tablets each.

Linaxa M XR Tablets 5 mg +1000 mg

White to off-white coloured, biconvex, oval shaped, film coated tablets, plain on both sides. The excipients used are Microcrystalline Cellulose (Avicel PH 101), Povidone Sodium CMC–8M30, Purified Water, Isopropyl Alcohol, Hypromellose, Magnesium Stearate, Talc, Hydroxy Propyl Methyl Cellulose, Methylene Chloride, Meglumine, Polyethylene glycol 6000, Opadry Complete FCS 02H580032 White

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

Mfg. Licence No: M/563/2010

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/Linaxa M XR 5 mg/1000 mg/Jun-23/01/PI