## Linagliptin and Metformin Hydrochloride

# Lintor M 500®

2.5 mg/500 mg Film coated tablet
Antidiabetic Agent

**PRODUCT DESCRIPTION:**
Light Yellow, Oblong, biconvex, film-coated tablet with breakline scored on one side.

**FORMULATION/COMPOSITION:**
Each film-coated tablet contains:
Linagliptin.....2.5 mg
Metformin Hydrochloride.....500 mg

**INDICATIONS:**
Linagliptin is indicated in adult patients with type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise to improve glycaemic control:
- in patients inadequately controlled on their maximally tolerated dose of Metformin alone
- in combination with other medicinal products for the treatment of diabetes, including insulin, in patients inadequately controlled with Metformin and these medicinal products
- in patients already being treated with the combination of Linagliptin and Metformin as separate tablets.

**DOSAGE AND ADMINSTRATION:**
**Dosage:**
**Adults with normal renal function (GFR ≥ 90 mL/min)**
The dose of antihyperglycaemic therapy with Lintor M dose should be individualized based on current regimen, efficacy, and tolerability, not exceeding Linagliptin 5 mg/day plus Metformin hydrochloride 2000 mg/day.
**Patients inadequately controlled on maximal tolerated dose of Metformin monotherapy**
The usual starting dose of Lintor M should provide Linagliptin 2.5 mg twice daily (5 mg/day total) plus the same ongoing Metformin dose.
**Patients switching from co-administration of Linagliptin and Metformin**
Lintor M 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**
Lintor M should provide Linagliptin 2.5 mg twice daily (5 mg/day total) with Metformin at the same prior dose, and sulphonylurea dose reduction may be needed to reduce Hypoglycaemia risk.
**Patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of Metformin**
Lintor M should provide Linagliptin 2.5 mg twice daily (5 mg/day total) with Metformin equivalent to current dose, and insulin dose reduction may be needed to reduce Hypoglycaemia risk.

For the different doses of Metformin, Lintor M is available in strengths of 2.5 mg Linagliptin plus 500/850/1000 mg Metformin hydrochloride.

**Renal impairment**
Before initiating **Lintor M**, assess GFR for renal impairment and monitor at least annually (more frequently in elderly/high-risk patients); review lactic acidosis risk if GFR <60 mL/min, and if no adequate strength of Lintor M is available, use individual mono-components instead of the fixed-dose combination.
**Hepatic Impairment**
Lintor M is not recommended in patients with hepatic impairment due to the active substance Metformin. Clinical experience with Lintor M in patients with hepatic impairment is lacking.
**Elderly**
As Metformin is excreted by the kidney, Lintor M 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.
**Children and adolescents**
Lintor M is not recommended for use in children below 18 years due to lack of data on safety and efficacy.
**Missed dose**
If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken at the same day.

**Method of administration:**
Lintor M should be taken twice daily with meals to reduce Metformin-related gastrointestinal effects, alongside continued diet with regular carbohydrate distribution and energy restriction in overweight patients.

**CONTRAINDICATIONS:**
- Hypersensitivity to the active ingredient or any excipients
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma.
- Severe renal failure (GFR < 30 mL/min).
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock.
- 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

**SPECIAL WARNING AND PRECAUTIONS:**
**General**
Lintor M should not be used in patients with type 1 diabetes.
**Lactic acidosis**
Lactic acidosis is a rare but serious risk with Metformin due to drug accumulation, most often in renal impairment, acute cardiorespiratory disease, sepsis, dehydration, or mitochondrial disorders; patients should be educated and closely monitored for early symptoms such as acidotic dyspnea, abdominal pain, muscle cramps, asthenia, and hypothermia that may progress to coma, must be stopped immediately and urgent medical care sought if suspected, with diagnostic findings including low blood pH, elevated lactate, increased anion gap, and altered lactate/pyruvate ratio.
**Hypoglycaemia**
Hypoglycaemia risk increases when Lintor M is combined with sulphonylureas or insulin (dose reduction may be needed), while the risk remains low with Linagliptin + Metformin alone as these agents do not typically cause hypoglycaemia.
**Renal function**
GFR should be assessed before treatment initiation and regularly. 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**
In heart failure patients, heart failure increases risk of hypoxia and renal impairment; use Lintor M only in stable cases with monitoring and avoid in acute/unstable cases.
**Acute pancreatitis**
Acute pancreatitis has been observed in patients taking Linagliptin. If pancreatitis is suspected, Lintor M should be discontinued and if acute pancreatitis is confirmed, Lintor M should not be restarted.
**Bullous pemphigoid**
Bullous pemphigoid has been observed in patients taking Linagliptin. If bullous pemphigoid is suspected, Lintor M should be discontinued.
**Vitamin B12**
Metformin may reduce vitamin B12 levels; continue therapy if tolerated and not contraindicated, with appropriate treatment as per guidelines.

**USE IN SPECIFIC POPULATIONS:**
**Pregnancy, Lactation and Fertility**
**Pregnancy**
There are limited data from the use of Linagliptin in pregnant women and although Metformin shows no increased risk of congenital malformations in limited human data. As a precautionary measure, it is preferable to avoid the use of Lintor M if pregnancy is planned or confirmed.
**Lactation**
Lintor M is not recommended during breast-feeding as Metformin is excreted in small amounts in human milk and Linagliptin may also be excreted in animals; therefore, a decision should be made to either discontinue breast-feeding or stop/avoid therapy based on the benefit-risk balance for mother and child.
**Fertility**
No studies on the effect on human fertility have been conducted for Lintor M. No adverse effects on fertility were observed in animals up to the highest dose of 240 mg/kg/day (approximately 943 times human exposure based on AUC comparisons).

**ADVERSE REACTIONS:**
**Tabulated summary of adverse reactions**
Adverse reactions reported in all clinical trials with the Linagliptin+Metformin combination or the use of the monocomponents (Linagliptin or Metformin) in clinical trials or from post-marketing experience are shown below according to system organ class. Adverse reactions previously reported with one of the individual active substances may be potential adverse reactions with Lintor M, even if not observed in clinical trials with this medicinal product.

| System organ class | Adverse reaction | Frequency |
|---|---|---|
| **Infections and infestations** | Nasopharyngitis | Uncommon |
| **Immune system disorders** | Hypersensitivity (e.g. bronchial hyperreactivity) | Uncommon |
| **Metabolism and nutrition disorders** | Hypoglycaemia | Very common |
| | Lactic acidosis | Very rare |
| | Vitamin B12 decrease/ deficiency | Common |
| **Nervous system disorders** | Taste disturbance | Common |
| **Respiratory, thoracic and mediastinal disorders** | Cough | Uncommon |
| **Gastrointestinal disorders** | Decreased appetite | Uncommon |
| | Diarrhoea | Common |
| | Nausea | Common |

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|---|---|---|
| **Gastrointestinal disorders** | Pancreatitis | Rare |
| | Vomiting | Uncommon |
| | Constipation | Uncommon |
| | Abdominal pain | Very common |
| | Liver function disorders | 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 |

**OVERDOSE**

**Linagliptin**

**Symptoms**

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 observed with Metformin hydrochloride doses of up to 85 g, although lactic acidosis may occur in overdose or risk situations. This is a medical emergency requiring hospital treatment, and haemodialysis is the most effective method to remove lactate and Metformin.

**Therapy**

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.

**PHARMACOLOGICAL PROPERTIES:**

**Pharmacodynamic properties:**

Pharmacotherapeutic group: Combinations of oral blood glucose lowering drugs, ATC code: A10BD11

**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 glucose-dependently increases insulin secretion and lowers glucagon secretion thus resulting in an overall improvement in the glucose homeostasis. Linagliptin binds selectively to DPP-4 and exhibits a > 10 000 fold selectivity versus DPP-8 or DPP-9 activity in vitro.

**Metformin**

Metformin hydrochloride is a biguanide with 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 utilization,

(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 favorable 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.

**Pharmacokinetic properties:**

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

Administration of Linagliptin/Metformin hydrochloride 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 Lintor M.

**Linagliptin:**

The pharmacokinetics of Linagliptin has been extensively characterized 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 medicinal product. 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-4, 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 AUC0-72h 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 30-20% 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.

**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.

**STORAGE CONDITION:**

Store at or below 30°C

**AVAILABILITY:**

Alu-Alu blister pack x 10's (Box of 30's)

**MANUFACTURED BY:**

Quest Pharmaceuticals Pvt. Ltd.
Chhatapipara, Bara, Nepal.

**MARKETING AUTHORIZATION HOLDER:**

Quest Pharmaceuticals Pvt. Ltd.
Daan Sadan, Teku, Kathmandu, Nepal.