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LINAGLIPTIN

LINTOR 5®

5 mg Film coated tablet
Antidiabetic Agent

PRODUCT DESCRIPTION:

Light Red, round, biconvex film-coated tablet with "Q" logo scored on one side.

FORMULATION/COMPOSITION:

Each film-coated tablet contains:
Linagliptin.....................5 mg

INDICATIONS:

Linagliptin is indicated in adult patients with type 2 diabetes mellitus (T2DM) to improve glycaemic control in conjunction with diet and exercise, as monotherapy or as add on to metformin, sulphonylureas, thiazolidinediones, insulin (with or without metformin and/or pioglitazone and/or sulphonylurea) or metformin plus sulphonylureas or metformin plus SGLT2 inhibitors.

DOSAGE AND ADMINSTRATION:

Adults

The recommended dose is 5 mg once daily. Linagliptin (Lintor 5) can be taken with or without a meal at any time of the day.

Renal impairment

No dose adjustment is required for patients with renal impairment.

Hepatic Impairment

No dose adjustment is required for patients with hepatic impairment.

Elderly

No dose adjustment is necessary.

Children and adolescents

Linagliptin (Lintor 5) 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.

CONTRAINDICATIONS:

Hypersensitivity to the active ingredient or any excipients

SPECIAL WARNING AND PRECAUTIONS:

General

Linagliptin (Lintor 5) should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Pancreatitis

Acute pancreatitis has been observed in patients taking linagliptin If pancreatitis is suspected, Linagliptin (Lintor 5) should be discontinued.

Hypoglycaemia

Linagliptin alone showed a comparable incidence of hypoglycaemia to placebo.

In clinical trials of linagliptin as part of combination therapy with agents not known to cause hypoglycaemia (metformin, thiazolidinediones) rates of hypoglycaemia reported with linagliptin were similar to rates in patients taking placebo.

Sulphonylureas are known to cause hypoglycaemia. Therefore, caution is advised when linagliptin is used in combination with a sulphonylurea. A dose reduction of the sulphonylurea may be considered.

Bullous pemphigoid

Bullous pemphigoid has been observed in patients taking linagliptin. If bullous pemphigoid is suspected, Linagliptin (Linagliptin) should be discontinued.

USE IN SPECIFIC POPULATIONS:

Pregnancy, Lactation and Fertility

Pregnancy

There are limited data from the use of linagliptin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of Linagliptin (Lintor 5) during pregnancy.

Lactation

Available pharmacodynamic/toxicological data in animals have shown excretion of linagliptin/metabolites in milk. It is not known whether this drug is excreted in human milk. Caution should be exercised when Linagliptin (Lintor 5) is administered to a nursing woman.

Fertility

No studies on the effect on human fertility have been conducted for Linagliptin (Lintor 5). 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:

Adverse reactions reported in patients who received Linagliptin 5 mg daily as mono- or add-on therapy in clinical trials and adverse reactions identified from post-marketing experience

Infections and infestations:
Nasopharyngitis
Immune system disorders:
Hypersensitivity
Metabolism and nutrition disorders:
Hypoglycaemia
Respiratory, thoracic and mediastinal disorders:
Cough
Gastrointestinal disorders:
Pancreatitis, Constipation
Skin and subcutaneous tissue disorders:
Angioedema, Urticaria, Rash, Bullous pemphigoid

OVERDOSE

Symptoms

During controlled clinical trials in healthy subjects, single doses of up to 600 mg linagliptin (equivalent to 120 times the recommended dose) were well tolerated. There is no experience with doses above 600 mg in humans.

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 as required

PHARMACOLOGICAL PROPERTIES:

Pharmacodynamic properties:

Pharmacotherapeutic group: DPP-4 inhibitor, ATC code: A10BH05

Linagliptin is an inhibitor of the enzyme DPP-4 (Dipeptidyl peptidase 4, EC 3.4.14.5) 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 (Lintor 5) glucose-dependently increases insulin secretion and lowers glucagon secretion thus resulting in an overall improvement in the glucose homoeostasis. Linagliptin binds selectively to DPP-4 and exhibits a >10000-fold selectivity versus DPP-8 or DPP-9 activity in vitro.

Pharmacokinetic properties:

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.

STORAGE CONDITION:

Store at or below 30^{0}C

AVAILABILITY:

Alu-Alu blister pack x 10's (Box of 120's)

MANUFACTURED BY:

Quest Pharmaceuticals Pvt. Ltd.
Chhatapipara, Bara, Nepal

MARKETING AUTHORIZATION HOLDER:

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