

For the use only of Registered Medical Practitioner

1. Generic Name & Brand Name

Linagliptin Tablets 5 mg
Lingretin® 5

2. Qualitative and Quantitative Composition:

Each film coated tablet contains:

Linagliptin.....5 mg

Excipients.....q.s.

Colours: Titanium Dioxide I.P. & Ferric Oxide USP NF Red.

3. Dosage Form & strength

Refer section 1 & 2.

4. Clinical particulars

4.1 Therapeutic indication

As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Important limitations of use:

1. Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

4.2 Posology and method of administration

Posology

The dose of linagliptin is 5 mg once daily. When linagliptin is added to metformin, the dose of metformin should be maintained, and linagliptin administered concomitantly.

When linagliptin is used in combination with a Sulphonylureas or with insulin, a lower dose of the sulfonylurea or insulin, may be considered to reduce the risk of hypoglycaemia.

Special populations

- Renal impairment: For patients with renal impairment, no dose adjustment for linagliptin is required.
- Hepatic impairment: Pharmacokinetic studies suggest that no dose adjustment is required for patients with hepatic impairment but clinical experience in such patients is lacking.
- Elderly: No dose adjustment is necessary based on age.
- Paediatric population: The safety and efficacy of linagliptin in children and adolescents has not yet been established. No data are available.

Method of Administration: The tablets can be taken with or without a meal at any time of the day. If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

General

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

Hypoglycaemia

Linagliptin alone showed a comparable incidence of hypoglycaemia to placebo.

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

When linagliptin was added to a sulfonylurea (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 is used in combination with a sulfonylurea and/or insulin. A dose reduction of the sulfonylurea or insulin may be considered.

Acute pancreatitis

Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Acute pancreatitis has been observed in patients taking linagliptin. In a cardiovascular and renal safety study (CARMELINA) with median observation period of 2.2 years, adjudicated acute pancreatitis was reported in 0.3% of patients treated with linagliptin and in 0.1% of patients treated with placebo. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Lingretin® 5 should be discontinued; if acute pancreatitis is confirmed, Lingretin® 5 should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Bullous pemphigoid

Bullous pemphigoid has been observed in patients taking linagliptin. In the CARMELINA study, bullous pemphigoid was reported in 0.2% of patients on treatment with linagliptin and in no patient on placebo. If bullous pemphigoid is suspected, Lingretin® 5 should be discontinued.

4.5 Drug Interactions

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 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 co-administered medicinal products is low.

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

Ritonavir: co-administration of a single 5 mg oral dose of linagliptin and multiple 200 mg oral doses of ritonavir, a potent inhibitor of P-glycoprotein and CYP3A4, increased the AUC and C_{max} of linagliptin approximately twofold and threefold, respectively. The unbound concentrations, which are usually less than 1% at the therapeutic dose of linagliptin, were increased 4-5-fold after co-administration with ritonavir. Simulations of steady-state plasma concentrations of linagliptin with and without ritonavir indicated that the increase in exposure will be not 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.

Metformin: co-administration of multiple three times daily doses of 850 mg metformin with 10 mg linagliptin once daily did not clinically meaningfully alter the pharmacokinetics of linagliptin in healthy volunteers.

Sulphonylureas: the steady-state pharmacokinetics of 5 mg linagliptin was not changed by concomitant administration of a single 1.75 mg dose glibenclamide (glyburide).

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 medicinal product 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, an OCT substrate, had no relevant effect on the pharmacokinetics of metformin in healthy volunteers. Therefore, linagliptin is not an inhibitor of OCT-mediated transport.

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

Digoxin: co-administration of multiple daily doses of 5 mg linagliptin with multiple doses of 0.25 mg digoxin had no effect on the pharmacokinetics of digoxin in healthy volunteers. 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 volunteers. Following administration of a supratherapeutic dose of 10 mg linagliptin concomitantly with 40 mg of simvastatin daily for 6 days, the plasma AUC of simvastatin was increased by 34%, and the plasma C_{max} by 10%.

Oral contraceptives: co-administration with 5 mg linagliptin did not alter the steady-state pharmacokinetics of levonorgestrel or ethinylestradiol.

4.6 Use in special populations (Pregnancy, Nursing woman, Pediatric use, Geriatric use)

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. As a precautionary measure, it is preferable to avoid the use of linagliptin during pregnancy.

Breast-feeding

Available pharmacokinetic data in animals have shown excretion of linagliptin/metabolites in milk. A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from linagliptin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No studies on the effect on human fertility have been conducted for linagliptin. Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

Linagliptin has no or negligible influence on the ability to drive and use machines. However, patients should be alerted to the risk of hypoglycaemia especially when combined with sulfonylurea and/or insulin.

4.8 Undesirable effects

Summary of the safety profile

In the pooled analysis of the placebo-controlled trials, the overall incidence of adverse events in patients treated with placebo was similar to linagliptin 5 mg (63.4% versus 59.1%). Discontinuation of therapy due to adverse events was higher in patients who received placebo as compared to linagliptin 5 mg (4.3% versus 3.4%).

The most frequently reported adverse reaction was “hypoglycaemia” observed under the triple combination, linagliptin plus metformin plus Sulphonylureas 14.8% versus 7.6% in placebo.

In the placebo-controlled studies 4.9% of patients experienced “hypoglycaemia” as an adverse reaction under linagliptin. Of these, 4.0% were mild and 0.9% were moderate and 0.1% were classified as severe in intensity. Pancreatitis was reported more often in patients randomized to linagliptin (7 events in 6,580 patients receiving linagliptin versus 2 events in 4,383 patients receiving placebo).

Tabulated list of adverse reactions

Due to the impact of the background therapy on adverse reactions (e.g. on hypoglycaemias), adverse reactions were analysed based on the respective treatment regimens (monotherapy, add-on to metformin, add-on to metformin plus Sulphonylureas, and add-on to insulin).

The placebo-controlled studies included studies where linagliptin was given as

- monotherapy with short-term duration of up to 4 weeks
- monotherapy with ≥ 12 -week duration
- add-on to metformin
- add-on to metformin + sulfonylurea
- add on to metformin and empagliflozin
- add-on to insulin with or without metformin

Adverse reactions classified by system organ class and MedDRA preferred terms reported in patients who received 5 mg linagliptin in double-blind studies as monotherapy or as add-on therapy are presented in the table below (see table 1).

The adverse reactions are listed by absolute frequency. Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$), uncommon ($\geq 1/1,000$ to $<1/100$), rare ($\geq 1/10,000$ to $<1/1,000$), very rare ($<1/10,000$) or not known (cannot be estimated from the available data).

Table Adverse reactions reported in patients who received linagliptin 5 mg daily as monotherapy or as add-on 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

Respiratory, thoracic, and mediastinal disorders	
Cough	uncommon
Gastrointestinal disorders	
Pancreatitis	rare [#]
Constipation ²	uncommon
Skin and subcutaneous tissue disorders	
Angioedema*	rare
Urticaria*	rare
Rash*	uncommon
Bullous pemphigoid	rare [#]
Investigations	
Amylase increased	uncommon
Lipase increased**	common

* Based on post-marketing experience

** Based on lipase elevations >3xULN observed in clinical trials

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

1 Adverse reaction observed in combination with metformin plus sulfonylurea

2 Adverse reaction observed in combination with insulin

Linagliptin cardiovascular and renal safety study (CARMELINA)

The CARMELINA study evaluated the cardiovascular and renal safety of linagliptin versus placebo in patients with type 2 diabetes and with increased CV risk evidenced by a history of established macrovascular or renal disease (see section 5.1). The study included 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 study was in line with previous known safety profile of linagliptin.

In the treated population, severe hypoglycaemic events (requiring assistance) were reported in 3.0% of patients on linagliptin and in 3.1% on placebo. Among patients who were using sulfonylurea at baseline, the incidence of severe hypoglycaemia was 2.0% in linagliptin-treated patients and 1.7% in placebo treated patients. Among patients who were using insulin at baseline, the incidence of severe hypoglycaemia was 4.4% in linagliptin-treated patients and 4.9% in placebo treated patients.

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

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

4.9 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 generally 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 if required.

5. Pharmacological properties

Pharmacotherapeutic group: tablets contain 1 oral antihyperglycemic drugs used in the management of type 2 diabetes mellitus: Linagliptin

ATC Code: A10BD

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 insulintropic 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.

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

Absorption

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_{max} 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 dose-proportional 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.

Distribution

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.

Metabolism

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.

Elimination

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.

Excretion

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.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

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 1,500 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.

7. Description

Lingretin 5 is supplied for oral administration, as a film coated tablet of Linagliptin. Each tablet of Lingretin 5 contains 5 mg of Linagliptin.

Version No. 2.0, dated 30th May 2024

Replaces Version No. 1.0, dated 21st July 2023

8. Pharmaceutical particulars

8.1 Incompatibilities

Not Applicable

8.2 Shelf Life

Refer Pack

8.3 Packaging Information

Refer Pack

8.4 Storage and handling instructions

Refer Pack

9. Patient Counseling Information

- What is Linagliptin Tablets?
Linagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- When should you not take Linagliptin Tablets?
If you are allergic to Linagliptin Tablets or any of the other ingredients of this medicine. If you think you may be allergic to Linagliptin Tablets or any of the other ingredients of Linagliptin Tablets, do not take this medicine and talk to your doctor.
Warnings and precautions
 - When used with an insulin secretagogue (e.g., sulfonylurea), consider lowering the dose of the insulin secretagogue to reduce the risk of hypoglycemia
 - There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Linagliptin or any other antidiabetic drug.
- If you have taken too many tablets?
Contact your doctor immediately or go to the nearest hospital casualty department taking any remaining medication and this patient information leaflet with you.
- If you forget to take Tablet?
If you miss a dose of Tablet, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular schedule. Do not double the dose.
- What are the possible side effects of Linagliptin?
Nasopharyngitis, Hypoglycemia, sometimes, Stomach Pain and eyes and Skin turns yellow although this may be less obvious on brown or black skin – this can be a sign of liver problems.

10. Details of manufacturer

Refer Pack for manufacturers details.

Marketed by:

Abbott Healthcare Pvt. Ltd.

Angel Space, Bldg. D-4, Gala No. 1 to 6 &

11 to 16 Ground Floor, 101 to 106 &

111 to 116 First Floor, 201 to 206 & 211 to 216

2nd Floor, Pimplas, Dist. Thane, Bhiwandi - 421 302, India.

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11. Details of permission or licence number with date

Version No. 2.0, dated 30th May 2024

Replaces Version No. 1.0, dated 21st July 2023

Refer pack for permission/License details

12. Date of revision

Version 2.0, dated 30/05/2024

For Product Complaints/Adverse events or Queries please write to webmasterindia@abbott.com