

1. NAME OF THE MEDICINAL PRODUCT

Glaxiprix Film-Coated Tablet 5mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of linagliptin.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dosage form: Film-coated tablet

Light pink, round, biconvex film-coated tablet debossed with '5' on one side. The diameter of the tablet is 8.1 mm \pm 5% (7.7-8.5) mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Glaxiprix is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, as monotherapy only.

4.2 Posology and method of administration

Posology

The dose of linagliptin is 5 mg once daily.

Special populations

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

A clinical trial did not establish efficacy in paediatric patients 10 to 17 years of age. Therefore, treatment of children and adolescents with linagliptin is not recommended. Linagliptin has not been studied in paediatric patients under 10 years of age.

Method of administration

Glaxiprix 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

Glaxiprix 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, Glaprixa should be discontinued.

Hypoglycaemia

Linagliptin alone showed a comparable incidence of hypoglycaemia to placebo.

Bullous pemphigoid

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic Interaction

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

The risk for clinically meaningful interactions by co-administered medicinal products is low.

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.

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.

Effects of linagliptin on other medicinal products

Linagliptin had no clinically relevant effect on the pharmacokinetics of, 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).

Digoxin: Co-administration of multiple 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 Fertility, pregnancy and lactation

Pregnancy

The use of linagliptin has not been studied in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of Glaprixa during pregnancy.

Breast-feeding

Available pharmacokinetic data in animals have shown excretion of linagliptin/metabolites in milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Glaprixa therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

It is not known whether this drug is excreted in human milk. Caution should be exercised when Glaprixa is administered to a nursing woman.

Fertility

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be alerted to the risk of hypoglycaemia.

4.8 Undesirable effects

Summary of the safety profile

The safety of linagliptin has been evaluated in patients with Type 2 Diabetes Mellitus, which in most cases received the target dose of 5 mg.

Tabulated summary of adverse reactions:

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 $< 1/1,000$), or very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

<i>MedDRA System Organ Class terminology</i>	<i>Linagliptin Adverse reactions</i>	<i>Frequency</i>
Infections & infestations	Nasopharyngitis	Uncommon
Immune system disorders	Hypersensitivity	Uncommon
	Angioedema ¹	Rare
	Urticaria ¹	Rare

Respiratory, thoracic & mediastinal disorders	Cough	Uncommon
Gastrointestinal disorders	Pancreatitis	Uncommon
	Mouth ulceration ¹	Rare
Skin and subcutaneous tissue disorders	Rash ¹	Uncommon
	Bullous pemphigoid ^{1;4}	Rare
Investigations	Lipase increased ²	Common
	Amylase increased ³	Uncommon

¹ ADR identified based on post-marketing experience

² Based on lipase elevations > 3xULN observed in clinical trials

³ See also *Linagliptin safety study* below.

Linagliptin safety study

The study evaluated the safety of linagliptin versus placebo in patients with type 2 diabetes and with increased CV risk evidenced by a history of established macrovascular disease.

In the treated population, severe hypoglycaemic events (requiring assistance) were reported in 3.0% of patients on linagliptin and in 3.1% on placebo.

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.

Bullous pemphigoid was reported in 0.2% of patients treated with linagliptin and in no patient treated with placebo.

4.9 Overdose

Symptoms

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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, dipeptidyl peptidase 4 (DPP-4) inhibitor, ATC code: A10BH05

Mechanism of action

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 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*.

5.2 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 T_{max}) occurring 1.5 hours post-dose.

Plasma concentrations of linagliptin decline in at least a biphasic 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 C_{max} by 2 hours and lowered C_{max} by 15% but no influence on AUC_{0-72h} was observed. No clinically relevant effect of C_{max} and T_{max} changes is expected; therefore linagliptin may be administered with or without food.

Distribution

As a result of tissue binding, the mean apparent volume of distribution at steady-state following a single 5 mg intravenous dose of linagliptin to healthy subjects is approximately 1110 litres, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration dependent, decreasing from about 99% at 1 nmol/l to 75-89% at ≥ 30 nmol/l, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70-80% of linagliptin was bound to other plasma proteins than DPP-4, hence 20-30% were unbound in plasma.

Biotransformation

Following a [^{14}C] 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.

Excretion

Following administration of an oral [^{14}C] 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.

Special populations

Hepatic impairment

In non-diabetic patients with mild moderate and severe hepatic impairment (according to the Child-Pugh classification), mean AUC and C_{max} of linagliptin were similar to healthy matched controls following administration of multiple 5 mg doses of linagliptin. No dosage adjustment for linagliptin is proposed for diabetic patients with mild, moderate or severe hepatic impairment.

Body Mass Index (BMI)

No dosage adjustment is necessary based on BMI. Body mass index had no clinically relevant effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. The clinical trials before marketing authorization have been performed up to a BMI equal to 40 kg/m².

Gender

No dosage adjustment is necessary based on gender. Gender had no clinically relevant effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis.

Geriatric

No dosage adjustment is required based on age up to 80 years, as age did not have a clinically relevant impact on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. Elderly subjects (65 to 80 oldest patients was 78 years) had comparable plasma concentrations of linagliptin compared to younger subjects.

Paediatric population

Pharmacokinetics and pharmacodynamics of 1 mg and 5 mg linagliptin were investigated in children and adolescents 10 to 17 years of age with type 2 diabetes mellitus. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects. Linagliptin 5 mg showed superiority over 1 mg with regard to trough DPP-4 inhibition (72% vs 32%, p=0.0050) and a numerically larger reduction with regard to placebo-corrected adjusted mean change from baseline in HbA1c (-0.63% vs -0.48%, n.s.) after 12 weeks.

Pharmacokinetics and pharmacodynamics (HbA1c change from baseline) of 5 mg linagliptin were investigated in children and adolescents 10 to 17 years of age with type 2 diabetes mellitus. The observed exposure-response relationship was overall comparable in paediatric and adult patients. Oral administration of linagliptin resulted in exposure within the range observed in adult patients. The observed geometric mean trough concentrations and geometric mean concentrations at 1.5 hours post-administration at steady state were 4.30 nmol/L and 12.6 nmol/L, respectively.

Race

No dosage adjustment is necessary based on race.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Crospovidone
Hypromellose
Silica colloidal anhydrous
Magnesium stearate
Water, purified

Film coating

Hypromellose
Titanium dioxide
Talc
Macrogol
Red iron oxide

6.2 Storage condition

Do not store above 30°C.

6.3 Nature and contents of container

Glaxipria film-coated tablets are packed in Aluminium-OPA/Alu/PVC blisters. The blister foil of the packaging system consists of an OPA/Alu/PVC base film sealed against an aluminium lidding foil. The blisters are packed into carton boxes along with the package insert.

Pack size of 30's film-coated tablets.

7. PRODUCT REGISTRATION HOLDER

Sandoz Products Malaysia Sdn. Bhd.
Unit 1202, Level 12, Uptown 1,
No. 1, Jalan SS 21/58
Damansara Uptown,
47400 Petaling Jaya,
Selangor.

10. DATE OF REVISION OF THE TEXT

February 2026

Package insert will be presented in font size 10, measure in Times New Roman