Linglor® 5

Linagliptin

FORMS AND PRESENTATION

Linglor®5: Film Coated Tablets: Box of 30.

COMPOSITION

Linglor®5: Each film coated tablet contains Linagliptin 5mg.

Excipients: mannitol, maize starch, povidone, magnesium stearate, hypromellose, iron oxide red, titanium dioxide, macrogol.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, dipeptidyl peptidase 4 (DPP-4) inhibitors, 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.

Pharmacokinetic properties

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 patients is approximately 1 110 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 [^{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.

Elimination

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

Renal impairment

Under steady-state conditions, linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects. In moderate renal impairment, a moderate increase in exposure of about 1.7 fold was observed compared with control. Exposure in T2DM patients with severe renal impairment was increased by about 1.4 fold compared to T2DM patients with normal renal function. Steady-state predictions for AUC of linagliptin in patients with ESRD indicated comparable exposure to that of patients with moderate or severe renal impairment. In addition, linagliptin is not expected to be eliminated to a therapeutically significant degree by hemodialysis or peritoneal dialysis. Therefore, no dosage adjustment of linagliptin is necessary in patients with any degree of renal insufficiency.

Hepatic impairment

In non-diabetic patients with mild moderate and severe hepatic insufficiency (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. BMI had no clinically relevant effect on the pharmacokinetics of linagliptin.

Elderly

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. Older subjects (65 to 80 years) had comparable plasma concentrations of linagliptin compared to younger subjects. Linagliptin trough concentrations were also measured in elderly (age ≥ 70 years) with type 2 diabetes and were within the range of values previously observed in younger type 2 diabetes patients.

Paediatric population

The observed exposure-response relationship was generally comparable between paediatric and adult patients, however, with a smaller drug effect estimated in children. 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 (representing a concentration around T_{max}) at steady state were 4.30 nmol/L and 12.6 nmol/L, respectively. Corresponding plasma concentrations in adult patients were 6.04 nmol/L and 15.1 nmol/L.

INDICATIONS

Linglor®5 is indicated in adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control as:

• monotherapy when metformin is inappropriate due to intolerance, or contraindicated due to renal impairment.

•combination therapy with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control.

CONTRAINDICATIONS

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

PRECAUTIONS

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

Hypoglycaemia

Sulphonylureas and insulin are known to cause hypoglycaemia. Therefore, caution is advised when linagliptin is used in combination with a sulphonylurea and/or insulin. A dose reduction of the sulphonylurea 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. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Linglor®5 should be discontinued; if acute pancreatitis is confirmed, Linglor®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. If bullous pemphigoid is suspected, Linglor®5 should be discontinued.

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 sulphonylurea and/or insulin.

PREGNANCY AND LACTATION

Pregnancy

The use of linagliptin has not been studied in pregnant women. As a precautionary measure, it is preferable to avoid the use of linagliptin during pregnancy.

Breast-feeding

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 considering the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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
Rifampicin: multiple co-administration of 5 mg linagliptin with rifampicin, a potent inductor 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 not be 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 patients.
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
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).

ADVERSE EFFECTS
The adverse reactions are listed by absolute frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) or not known (cannot be estimated from the available data).
Infections and infestations: nasopharyngitis (uncommon).
Immune system disorders: hypersensitivity (e.g. bronchial hyperreactivity) (uncommon).
Metabolism and nutrition disorders: hypoglycaemia (very common).
Respiratory, thoracic and mediastinal disorders: cough (uncommon).
Gastrointestinal disorders: constipation (uncommon), pancreatitis (rare).
Skin and subcutaneous tissue disorders: rash (uncommon), angioedema, urticaria, bullous pemphigoid (rare).
Investigations: lipase increased (common), amylase increased (uncommon).

Adverse reactions observed in combination with metformin plus sulphonylureas and in combination with insulin
Severe hypoglycaemic events were reported in patients who were using sulfonylurea or insulin at baseline.
Paediatric population
In paediatric patients with type 2 diabetes mellitus aged 10 to 17 years, the safety profile of linagliptin was similar to that observed in the adult population.

Reporting of Suspected Adverse Reactions
Pharmacovigilance involves monitoring and evaluating the safety of pharmaceutical products to ensure that any adverse reaction or problem related to the use of this medicine is identified and managed appropriately.
If you experience any adverse reaction or side effect while using this product, please report it immediately to Benta S.A.L through one of the following means:
Telephone: +961 4 545000
E-mail: PV@benta-group.com

DOSAGE AND ADMINISTRATION
Posology
The dose of Linglor®5 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 sulphonylurea or with insulin, a lower dose of the sulphonylurea 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
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
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.

OVERDOSAGE
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.

STORAGE CONDITIONS
Store below 30℃.
Keep in original pack in intact conditions.

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Marketing Authorization Holder & Manufacturer
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