1. NAME OF THE MEDICINAL PRODUCT

Trajenta 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of linagliptin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

8 mm diameter round, light red film-coated tablet debossed with "D5" on one side and the Boehringer Ingelheim logo on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Trajenta 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
- in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations).

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 sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin, may be considered to reduce the risk of hypoglycaemia (see section 4.4)

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.
However, clinical experience in patients > 80 years of age is limited and caution should be exercised when treating this population.

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 listed in section 6.1.

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 sulphonylurea (on a background of metformin), the incidence of hypoglycaemia was increased over that of placebo (see section 4.8).

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 (see section 4.2).

Acute pancreatitis
Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. In post-marketing experience of linagliptin there have been spontaneously reported adverse reactions of acute pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Trajenta should be discontinued; if acute pancreatitis is confirmed, Trajenta should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Bullous pemphigoid
There have been post-marketing reports of bullous pemphigoid in patients taking linagliptin. If bullous pemphigoid is suspected, Trajenta should be discontinued.

4.5 Interaction with other medicinal products and other forms of 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
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 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 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 clinical 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 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 (see section 5.3). 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 (see section 5.3).

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 sulphonylurea 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 sulphonylurea 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. 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 and displayed based on the respective treatment regimens (monotherapy, add-on to metformin, add-on to meformin plus sulphonylurea, 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 + sulphonylurea
- 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 per treatment regimen in the table below (see table 1).

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).

Table 1 Adverse reactions reported in patients who received linagliptin 5 mg daily as monotherapy or as add-on therapies (frequencies identified from pooled analysis of placebo-controlled studies) in clinical trial and from post-marketing experience

	Adverse reactions by treatment regimen				
System organ class Adverse reaction	Linagliptin monotherapy	Linagliptin + Metformin	Linagliptin + Metformin + Sulphonylurea	Linagliptin + Insulin	Linagliptin + Metformin + Empagliflozin
Infections and infestations					
Nasopharyngitis	uncommon	uncommon	not known	uncommon	not known
Immune system disorders					
Hypersensitivity (e.g. bronchial hyperreactivity)	uncommon	uncommon	uncommon	uncommon	not known
Metabolism and nutrition disorders					
Hypoglycaemia			very common		
Respiratory, thoracic and mediastinal disorders					
Cough	uncommon	uncommon	not known	uncommon	not known
Gastrointestinal disorders					
Pancreatitis	not known	not known	not known	uncommon	not known
Constipation				uncommon	
Skin and subcutaneous tissue disorders					
*Angioedema**	rare				
*Urticaria**	rare				
*Rash**	uncommon				
*Bullous pemphigoid**	not known				
Investigations					
Amylase increased	rare	uncommon	uncommon	not known	uncommon
*Lipase increased***	common	common	common	common	common

* Based on post-marketing experience
** Based on lipase elevations >3xULN observed in clinical trials

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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

5.1 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 peptide1, 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*.

Clinical efficacy and safety
8 phase III randomised controlled trials involving 5,239 patients with type 2 diabetes, of which 3,319 were treated with linagliptin were conducted to evaluate efficacy and safety. These studies had 929 patients of 65 years and over who were on linagliptin. There were also 1,238 patients with mild renal impairment, and 143 patients with moderate renal impairment on linagliptin. Linagliptin once daily produced clinically significant improvements in glycaemic control, with no clinically relevant change in body weight. The reductions in glycosylated haemoglobin A1c (HbA1c) were similar across different subgroups including gender, age, renal impairment and body mass index (BMI). Higher baseline HbA1c was associated with a greater reduction in HbA1c. There was a significant difference in reduction in HbA1c between Asian patients (0.8%) and White patients (0.5%) in the pooled studies.

Linagliptin as monotherapy in patients ineligible for metformin
The efficacy and safety of linagliptin monotherapy was evaluated in a double-blind placebo-controlled study of 24 weeks duration. Treatment with once daily linagliptin at 5 mg provided a significant improvement in HbA1c (-0.69% change compared to placebo), in patients with baseline HbA1c of approximately 8%. Linagliptin also showed significant improvements in fasting plasma glucose

(FPG), and 2-hour post-prandial glucose (PPG) compared to placebo. The observed incidence of hypoglycaemia in patients treated with linagliptin was similar to placebo.

The efficacy and safety of linagliptin monotherapy was also evaluated in patients for whom metformin therapy is inappropriate, due to intolerability or contraindicated due to renal impairment, in a double-blind placebo-controlled study of 18 weeks duration. Linagliptin provided significant improvements in HbA1c, (-0.57% change compared to placebo), from a mean baseline HbA1c of 8.09%. Linagliptin also showed significant improvements in fasting plasma glucose (FPG) compared to placebo. The observed incidence of hypoglycaemia in patients treated with linagliptin was similar to placebo.

Linagliptin as add-on to metformin therapy
The efficacy and safety of linagliptin in combination with metformin was evaluated in a double-blind placebo-controlled study of 24 weeks duration. Linagliptin provided significant improvements in HbA1c, (-0.64% change compared to placebo), from a mean baseline HbA1c of 8%. Linagliptin also showed significant improvements in fasting plasma glucose (FPG), and 2-hour post-prandial glucose (PPG) compared to placebo. The observed incidence of hypoglycaemia in patients treated with linagliptin was similar to placebo.

Linagliptin as add-on to a combination of metformin and sulphonylurea therapy
A placebo-controlled study of 24 weeks in duration was conducted to evaluate the efficacy and safety of linagliptin 5 mg to placebo, in patients not sufficiently treated with a combination with metformin and a sulphonylurea. Linagliptin provided significant improvements in HbA1c (-0.62% change compared to placebo), from a mean baseline HbA1c of 8.14%. Linagliptin also showed significant improvements in patients fasting plasma glucose (FPG), and 2-hour post-prandial glucose (PPG), compared to placebo.

Linagliptin as add-on to a combination of metformin and empagliflozin therapy
In patients inadequately controlled with metformin and empagliflozin (10 mg (n=247) or 25 mg (n=217)), 24-weeks treatment with add-on therapy of linagliptin 5 mg provided adjusted mean HbA1c reductions from baseline by -0.53% (significant difference to add-on placebo -0.32% (95% CI -0.52, -0.13) and -0.58% (significant difference to add-on placebo -0.47% (95% CI -0.66; -0.28), respectively. A statistically significant greater proportion of patients with a baseline HbA1c ≥7.0% and treated with linagliptin 5 mg achieved a target HbA1c of <7% compared to placebo.

Linagliptin as add-on to insulin therapy
The efficacy and safety of the addition of linagliptin 5 mg to insulin alone or in combination with metformin and/or pioglitazone has been evaluated in a double-blind placebo-controlled study of 24 weeks duration. Linagliptin provided significant improvements in HbA1c (-0.65% compared to placebo) from a mean baseline HbA1c of 8.3%. Linagliptin also provided significant improvements in fasting plasma glucose (FPG), and a greater proportion of patients achieved a target HbA1c of < 7.0%, compared to placebo. This was achieved with a stable insulin dose (40.1 IU). Body weight did not differ significantly between the groups. Effects on plasma lipids were negligible. The observed incidence of hypoglycaemia in patients treated with linagliptin was similar to placebo (22.2% linagliptin; 21.2% placebo).

Linagliptin 24 month data, as add-on to metformin in comparison with glimepiride
In a study comparing the efficacy and safety of the addition of linagliptin 5 mg or glimepiride (mean dose 3 mg) in patients with inadequate glycaemic control on metformin monotherapy, mean reductions in HbA1c were -0.16% with linagliptin (mean baseline HbA1c 7.69%) and -0.36% with glimepiride (mean baseline HbA1c 7.69%.) with a mean treatment difference of 0.20% (97.5% CI: 0.09, 0.299). The incidence of hypoglycaemia in the linagliptin group (7.5%) was significantly lower than that in the glimepiride group (36.1%). Patients treated with linagliptin exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glimepiride (-1.39 vs +1.29 kg).

Linagliptin as add-on therapy in patients with severe renal impairment, 12 week placebo-controlled data (stable background) and 40 week placebo-controlled extension (adjustable background)

The efficacy and safety of linagliptin was also evaluated in type 2 diabetes patients with severe renal impairment in a double-blind study versus placebo for 12 weeks duration, during which background glycaemic therapies were kept stable. Most patients (80.5%) received insulin as background therapy, alone or in combination with other oral anti-diabetics such as sulphonylurea, glinide and pioglitazone. There was a further follow up 40 week treatment period during which dose adjustments in antidiabetes background therapies were allowed.

Linagliptin provided significant improvements in HbA1c (-0.59 % change compared to placebo after 12 weeks), from a mean baseline HbA1c of 8.2%. The observed difference in HbA1c over placebo was -0.72% after 52 weeks.

Body weight did not differ significantly between the groups. The observed incidence of hypoglycaemia in patients treated with linagliptin was higher than placebo, due to an increase in asymptomatic hypoglycaemic events. There was no difference between groups in severe hypoglycaemic events.

Linagliptin as add-on therapy in elderly (age ≥ 70 years) with type 2 diabetes
The efficacy and safety of linagliptin in elderly (age ≥ 70years) with type 2 diabetes was evaluated in a double-blind study of 24 weeks duration. Patients received metformin and/or sulphonylurea and/or insulin as background therapy. Doses of background antidiabetic medicinal products were kept stable during the first 12 weeks, after which adjustments were permitted. Linagliptin provided significant improvements in HbA1c (-0.64 % change compared to placebo after 24 weeks), from a mean baseline HbA1c of 7.8%. Linagliptin also showed significant improvements in fasting plasma glucose (FPG) compared to placebo. Body weight did not differ significantly between the groups.

Cardiovascular (CV) risk
In a prospective meta-analysis of independently adjudicated CV events from 19 clinical studies (ranging from 18 weeks to 24 months duration) involving 9,459 patients with type 2 diabetes, linagliptin treatment was not associated with an increase in CV risk. The primary endpoint, the composite of: the occurrence or time to first occurrence of CV death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for unstable angina, was non-significantly lower for linagliptin versus combined active and placebo comparators [Hazard ratio 0.78 (95% confidence interval 0.55;1.12)]. In total there were 60 primary events on linagliptin and 62 on comparators. To date there is no evidence for an increased CV risk but the number of events in the clinical studies precludes firm conclusions. However, CV events were similar between linagliptin and placebo (1.03% with linagliptin vs 1.35% with placebo).

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with linagliptin in one or more subsets of the paediatric population in Type 2 diabetes (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of linagliptin has been extensively characterised 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 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 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 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.

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

Renal impairment
A multiple-dose, open-label study was conducted to evaluate the pharmacokinetics of linagliptin (5 mg dose) in patients with varying degrees of chronic renal insufficiency compared to normal healthy control subjects. The study included patients with renal insufficiency classified on the basis of creatinine clearance as mild (50 to <80 ml/min), moderate (30 to <50 ml/min), and severe (<30 ml/min), as well as patients with ESRD on hemodialysis. In addition patients with T2DM and severe renal impairment (<30 ml/min) were compared to T2DM patients with normal renal function. Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula. CrCl = (140 – age) x weight/72 x serum creatinine [x 0.85 for females], where age is in years, weight in kg, and serum creatinine is in mg/dl. 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 RI 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 based on a population pharmacokinetic analysis of Phase I and Phase II data. The clinical trials before marketing authorisation have been performed up to a BMI equal to 40 kg/m^2.

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 of Phase I and Phase II data.

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 based on a population pharmacokinetic analysis of Phase I and Phase II data. Older subjects (65 to 80, oldest patient was 78 years) had comparable plasma concentrations of linagliptin compared to younger subjects.

Paediatric population
A paediatric Phase 2 study examined the pharmacokinetics and pharmacodynamics of 1 mg and 5 mg linagliptin in children and adolescents ≥10 to <18 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 adjusted mean change from baseline in HbA1c (-0.63% vs -0.48%, n.s.). Due to the limited nature of the data set the results should be interpreted cautiously.

Race
No dosage adjustment is necessary based on race. Race had no obvious effect on the plasma concentrations of linagliptin based on a composite analysis of available pharmacokinetic data, including patients of Caucasian, Hispanic, African, and Asian origin. In addition the pharmacokinetic characteristics of linagliptin were found to be similar in dedicated phase I studies in Japanese, Chinese and Caucasian healthy volunteers.

5.3 Preclinical safety data

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Mannitol
Pregelatinised starch (maize)
Maize starch
Copovidone
Magnesium stearate

Film coating
Hypromellose
Titanium dioxide (E171)
Talc
Macrogol (6000)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C. Store in a safe place out of reach of children

6.5 Nature and contents of container

Perforated alu/alu unit dose blisters in cartons containing 10 x 1, 14 x 1, 28 x 1, 30 x 1, 56 x 1, 60 x 1, 84 x 1, 90 x 1, 98 x 1, 100 x 1 and 120 x 1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/707/001 (10 x 1 tablets)
EU/1/11/707/002 (14 x 1 tablets)
EU/1/11/707/003 (28 x 1 tablets)
EU/1/11/707/004 (30 x 1 tablets)
EU/1/11/707/005 (56 x 1 tablets)
EU/1/11/707/006 (60 x 1 tablets)
EU/1/11/707/007 (84 x 1 tablets)
EU/1/11/707/008 (90 x 1 tablets)
EU/1/11/707/009 (98 x 1 tablets)
EU/1/11/707/010 (100 x 1 tablets)
EU/1/11/707/011 (120 x 1 tablets)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 August 2011
Date of latest renewal: 22 March 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.