

TRAJENTAMET[®]

(Linagliptin and Metformin hydrochloride)

2.5mg/500mg, 2.5mg/850mg, 2.5mg/1000mg

NAME OF THE MEDICINE

TRAJENTAMET contains two oral antihyperglycaemic drugs used in the management of type 2 diabetes mellitus: linagliptin (a dipeptidyl peptidase-4 (DPP-4) inhibitor) and metformin hydrochloride.

Linagliptin

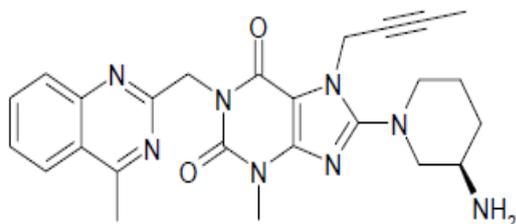
Chemical name: 1H-Purine-2, 6-dione, 8-[(3R)-3-amino-1-piperidiny]-7-(2-butyn-1-yl)-3,7-dihydro-3- methyl-1-[(4-methyl-2-quinazoliny)methyl]-

Molecular formula: C₂₅H₂₈N₈O₂

CAS number: 668270-12-0

Molecular weight: 472.54

Structural formula:



Metformin hydrochloride

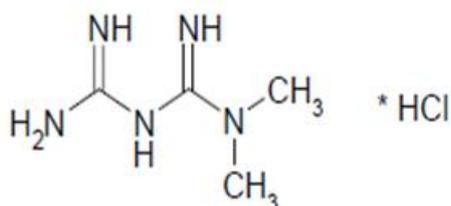
Chemical name: 1,1-dimethylbiguanide hydrochloride

Molecular formula: C₄H₁₁N₅.HCl

CAS number: 1115-70-4

Molecular weight: 165.63

Structural formula:



DESCRIPTION

Linagliptin is a white to yellowish, not or only slightly hygroscopic solid substance. It is very slightly soluble in water. Linagliptin is soluble in methanol, sparingly soluble in ethanol, very slightly soluble in isopropanol and very slightly soluble in acetone. Dissociation Constants: pK_{a1} = 8.6; pK_{a2} = 1.9. Partition Co-efficient: Log P = 1.7 (free base); Log D (pH 7.4) = 0.4.

Metformin hydrochloride is a white to off-white crystalline compound. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

TRAJENTAMET are film-coated tablets for oral administration

- TRAJENTAMET 2.5 mg/500 mg contains 2.5 mg linagliptin and 500 mg metformin hydrochloride
- TRAJENTAMET 2.5 mg/850 mg contains 2.5 mg linagliptin and 850 mg metformin hydrochloride
- TRAJENTAMET 2.5 mg/1000 mg contains 2.5 mg linagliptin and 1000 mg metformin hydrochloride

Each film-coated tablet of TRAJENTAMET contains the following inactive ingredients: arginine, starch maize, copovidone, silica - colloidal anhydrous, magnesium stearate, titanium dioxide, propylene glycol, hypromellose, talc - purified, iron oxide yellow (TRAJENTAMET 2.5 mg/500 mg; TRAJENTAMET 2.5 mg/850 mg) and/or iron oxide red (TRAJENTAMET 2.5 mg/850 mg; TRAJENTAMET 2.5 mg/1000 mg).

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: Combinations of oral blood glucose lowering drugs, ATC code: A10BD11

Linagliptin is an inhibitor of the enzyme DPP-4 (Dipeptidyl peptidase 4) 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 binding to DPP-4 is reversible but long lasting and thus leads to a sustained increase and a prolongation of active incretin levels. *In vitro*, linagliptin inhibits DPP-4 with nanomolar potency and exhibits a > 10000 fold selectivity versus DPP-8 or DPP-9 activity.

Metformin hydrochloride is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin hydrochloride may act via 3 mechanisms:

- (1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- (2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- (3) and delay of intestinal glucose absorption

Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin hydrochloride increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.

In humans, independently of its action on glycaemia, metformin hydrochloride has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin hydrochloride reduces total cholesterol, LDL cholesterol and triglyceride levels.

Pharmacokinetics

Bioequivalence studies in healthy subjects demonstrated that the TRAJENTAMET (linagliptin/metformin hydrochloride) combination tablets are bioequivalent to co-administration of linagliptin and metformin hydrochloride as individual tablets following a single dose.

Administration of TRAJENTAMET 2.5 mg/1000 mg with food resulted in no change in overall exposure of linagliptin. With metformin there was no change in AUC, however mean peak serum

concentration of metformin was decreased by 18% when administered with food. A delayed time to peak serum concentrations by 2 hours was observed for metformin under fed conditions. These changes are not likely to be clinically significant.

The following statements reflect the pharmacokinetic properties of the individual active substances of TRAJENTAMET.

Linagliptin

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 patients, linagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1.5 hours postdose.

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 drug. 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, steady-state plasma concentrations of 5 mg linagliptin 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).

Plasma AUC of linagliptin increased in a less than dose-proportional manner. The pharmacokinetics of linagliptin were generally similar in healthy subjects and in patients with type 2 diabetes.

Absorption

The absolute bioavailability of linagliptin is approximately 30%. Because co-administration of a high-fat meal with linagliptin had no clinically relevant effect on the pharmacokinetics, linagliptin may be administered with or without food. *In vitro* studies indicated that linagliptin is a substrate of P-glycoprotein and of CYP3A4. Ritonavir, a potent inhibitor of P-glycoprotein and CYP3A4, led to a twofold increase in exposure (AUC) and multiple co-administration of linagliptin with rifampicin, a potent inducer of P-glycoprotein and CYP3A, resulted in an about 40% decreased linagliptin steady-state AUC, presumably by increasing/decreasing the bioavailability of linagliptin by inhibition/induction of P-glycoprotein.

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 the peak plasma concentration in humans at 5 mg/day, approximately 10% of linagliptin is unbound.

Metabolism

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 and 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.

Metformin hydrochloride

Absorption

After an oral dose of metformin, T_{max} is reached in 2.5 hours. Absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin hydrochloride absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin hydrochloride absorption are non-linear.

At the recommended metformin hydrochloride doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 microgram/mL. In controlled clinical trials, maximum metformin hydrochloride plasma levels (C_{max}) did not exceed 5 microgram/mL, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin hydrochloride. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of the time to peak plasma concentration were observed. The clinical relevance of these decreases is unknown.

Distribution

Plasma protein binding is negligible. Metformin hydrochloride partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (Vd) ranged between 63-276 L.

Metabolism

Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism.

Elimination

Renal clearance of metformin hydrochloride is > 400 mL/min, indicating that metformin hydrochloride is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin hydrochloride in plasma.

Pharmacokinetics in special patient groups

Paediatric

Linagliptin

Studies characterising the pharmacokinetics of linagliptin in paediatric patients have not been performed.

Metformin hydrochloride

Single dose study: After single doses of metformin 500 mg, paediatric patients have shown a similar pharmacokinetic profile to that observed in healthy adults.

Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg twice daily for 7 days in paediatric patients the peak plasma concentration (C_{max}) and systemic exposure (AUC_{0-t}) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

Elderly

Linagliptin

No dosage adjustment is required based on age, 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 years) had comparable plasma concentrations of linagliptin compared to younger subjects.

Metformin hydrochloride

Limited data from controlled pharmacokinetic studies of metformin hydrochloride in healthy elderly subjects suggest that total plasma clearance of metformin hydrochloride is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin hydrochloride pharmacokinetics with aging is primarily accounted for by a change in renal function.

TRAJENTAMET treatment should not be initiated in patients \geq 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

Body Mass Index (BMI)

Linagliptin

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.

Gender

Linagliptin

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.

Metformin hydrochloride

Metformin hydrochloride pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analysed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycaemic effect of metformin hydrochloride was comparable in males and females.

Race

Linagliptin

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-American, 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 and African American type 2 diabetes patients.

Metformin hydrochloride

No studies of metformin hydrochloride pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin hydrochloride in patients with type 2 diabetes, the antihyperglycemic effect was comparable in white (n=249), black (n=51) and Hispanic (n=24) patients.

Renal impairment

Linagliptin

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 end stage renal disease (ESRD) on haemodialysis. In addition, patients with type 2 diabetes mellitus and severe renal impairment ($<$ 30 mL/min) were compared to patients with type 2 diabetes mellitus and 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: $CrCl = [140 - \text{age (years)}] \times \text{weight (kg)} \{ \times 0.85 \text{ for female patients} \} / [72 \times \text{serum creatinine (mg/dL)}]$.

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 patients with type 2 diabetes mellitus and severe renal insufficiency was increased by about 1.4 fold compared to patients with type 2 diabetes mellitus and 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 haemodialysis or peritoneal dialysis. Therefore, no dosage adjustment of linagliptin is necessary in patients with any degree of renal insufficiency. In addition, mild renal insufficiency had no effect on linagliptin pharmacokinetics in patients with type 2 diabetes mellitus as assessed by population pharmacokinetic analyses.

Metformin hydrochloride

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin hydrochloride is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic insufficiency

Linagliptin

In 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 necessary for patients with mild, moderate or severe hepatic insufficiency.

Metformin hydrochloride

No pharmacokinetic studies of metformin hydrochloride have been conducted in subjects with hepatic insufficiency.

CLINICAL TRIALS

Linagliptin as add- on to metformin therapy

The efficacy and safety of linagliptin in combination with metformin in patients with insufficient glycaemic control on metformin monotherapy was evaluated in a double blind placebo controlled study of 24 weeks duration.

Linagliptin added to metformin 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) by -1.2 mmol/L and 2-hour post-prandial glucose (PPG) by -3.7 mmol/L compared to placebo, as well as a greater portion of patients achieving a target HbA1c of < 7.0% (28.3% on linagliptin vs. 11.4% on placebo). The observed incidence of hypoglycaemia in patients treated with linagliptin was similar to placebo. Body weight did not differ significantly between the groups.

In a 24-week placebo-controlled factorial study of initial therapy, linagliptin 2.5 mg twice daily in combination with metformin (500 mg or 1000 mg twice daily) provided significant improvements in glycaemic parameters compared with either monotherapy as summarised in Table 1 (mean baseline HbA1c 8.65%).

Table 1: Glycaemic Parameters at Final Visit (24-Week Study) for Linagliptin and Metformin, Alone and in Combination in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Diet and Exercise

	Placebo	Linagliptin 5 mg Once Daily*	Metformin 500 mg Twice Daily	Linagliptin 2.5 mg Twice Daily* + Metformin 500 mg Twice Daily	Metformin 1000 mg Twice Daily	Linagliptin 2.5 mg Twice Daily* + Metformin 1000 mg Twice Daily
HbA1c (%)						
Number of patients	n = 65	n = 135	n = 141	n = 137	n = 138	n = 140
Baseline (mean)	8.7	8.7	8.7	8.7	8.5	8.7
Change from baseline (adjusted mean)	0.1	-0.5	-0.6	-1.2	-1.1	-1.6
Difference from placebo (adjusted mean) (95% CI)	--	-0.6 (-0.9, -0.3)	-0.8 (-1.0, -0.5)	-1.3 (-1.6, -1.1)	-1.2 (-1.5, -0.9)	-1.7 (-2.0, -1.4)
Patients (n, %) achieving HbA1c <7%	7 (10.8)	14 (10.4)	27 (19.1)	42 (30.7)	43 (31.2)	76 (54.3)
Patients (%) receiving rescue medication	29.2	11.1	13.5	7.3	8.0	4.3
FPG mmol/L						
Number of patients	n = 61	n = 134	n = 136	n = 135	n = 132	n = 136
Baseline (mean)	11.3	10.8	10.6	11.0	10.6	10.9
Change from baseline (adjusted mean)	0.6	-0.5	-0.9	-1.8	-1.8	-2.7
Difference from placebo (adjusted mean) (95% CI)	--	-1.1 (-1.7, -0.3)	-1.4 (-2.1, -0.8)	-2.4 (-3.1, -1.7)	-2.3 (-3.1, -1.7)	-3.3 (-4.0, -2.6)

* Total daily dose of linagliptin is equal to 5 mg; FPG – fasting plasma glucose

Mean reductions from baseline in HbA1c were generally greater for patients with higher baseline HbA1c values. Effects on plasma lipids were generally neutral. The decrease in body weight with the combination of linagliptin and metformin was similar to that observed for metformin alone or placebo; there was no change from baseline for patients on linagliptin alone. The incidence of hypoglycaemia was similar across treatment groups (placebo 1.4%, linagliptin 5 mg 0%, metformin 2.1%, and linagliptin 2.5 mg plus metformin twice daily 1.4%). In addition, this study included patients (n=66) with more severe hyperglycaemia (HbA1c at baseline \geq 11%) who were treated with twice daily open-label linagliptin 2.5 mg + metformin 1000 mg. In this group of patients, the mean baseline HbA1c value was 11.8% and mean FPG was 14.5 mmol/L. A mean decrease from baseline of -3.74% in HbA1c (n=48) and -4.5 mmol/L for FPG (n=41) was observed for patients completing the 24 week trial period without rescue therapy (n=48). In the LOCF analysis including all patients with primary endpoint measurements (n=65) at last observation without rescue therapy changes from baseline were -3.19% for HbA1c and -4.1 mmol/L for FPG.

The efficacy and safety of linagliptin 2.5 mg twice daily versus 5 mg once daily in combination with metformin in patients with insufficient glycaemic control on metformin monotherapy was evaluated in a double blind placebo controlled study of 12 weeks duration. Linagliptin (2.5 mg twice daily and 5 mg once daily) added to metformin provided significant improvements in glycaemic parameters

compared to placebo. Linagliptin 5 mg once daily and 2.5 mg twice daily provided comparable (CI: -0.07; 0.19), significant HbA1c reductions of -0.80% (from baseline 7.98%), and -0.74% (from baseline 7.96%) compared to placebo.

The observed incidence of hypoglycaemia in patients treated with linagliptin was similar to placebo (2.2% on linagliptin 2.5 mg twice daily, 0.9% on linagliptin 5 mg once daily, and 2.3% on placebo). Body weight did not differ significantly between the groups.

Linagliptin as add-on to a combination of metformin and sulfonylurea 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 controlled with a combination with metformin and a sulfonylurea. 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 achieving a target HbA1c of < 7.0% (31.2% on linagliptin vs. 9.2% on placebo), and also for fasting plasma glucose (FPG) with -0.7 mmol/L reduction compared to placebo. Body weight did not differ significantly between the groups.

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 (a sulfonylurea agent) in patients with inadequate glycaemic control on metformin monotherapy, linagliptin was similar to glimepiride in reducing HbA1c, with a mean treatment difference in HbA1c from baseline to 104 weeks for linagliptin compared to glimepiride of + 0.20%.

In this study, the proinsulin to insulin ratio, a marker of efficiency of insulin synthesis and release, showed a statistically significant improvement with linagliptin compared with glimepiride treatment. 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).

Cardiovascular risk

In a prospective, meta-analysis of independently adjudicated cardiovascular events from 17 phase III clinical studies involving 9462 patients with type 2 diabetes, linagliptin treatment was not associated with an increase in cardiovascular 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.

Cardiovascular events were observed to occur at a similar rate between linagliptin and placebo [Hazard ratio 1.09 (95% confidence interval 0.68;1.75)]. In placebo controlled studies, in total there were 43 (1.03%) primary events on linagliptin and 29 (1.35%) on placebo.

INDICATIONS

TRAJENTAMET is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate in patients inadequately controlled on metformin alone, or those already being treated and well controlled with the free combination of linagliptin and metformin.

TRAJENTAMET is indicated in combination with a sulfonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulfonylurea.

CONTRAINDICATIONS

- Hypersensitivity to active ingredients linagliptin and/or metformin hydrochloride or to any of the excipients
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma
- Renal failure or renal dysfunction (creatinine clearance < 60 mL/min), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicaemia
- Acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, recent myocardial infarction, shock
- Hepatic insufficiency, acute alcohol intoxication, alcoholism (due to the metformin component)

TRAJENTAMET should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials because use of such products may result in acute alteration of renal function (see **PRECAUTIONS - Administration of iodinated contrast agent**).

PRECAUTIONS

General

TRAJENTAMET should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis (see **CONTRAINDICATIONS**).

Pancreatitis

There have been post-marketing reports of acute pancreatitis in patients taking linagliptin. If pancreatitis is suspected, TRAJENTAMET should be discontinued.

Hypoglycaemia

Linagliptin alone showed a comparable incidence of hypoglycaemia to placebo. In clinical trials of linagliptin as part of combination therapy with agents not considered to cause hypoglycaemia (metformin, thiazolidinediones) rates of hypoglycaemia reported with linagliptin were similar to rates in patients taking placebo.

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

Metformin alone does not cause hypoglycaemia under usual circumstances of use, but hypoglycaemia could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol.

Lactic acidosis

Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin hydrochloride accumulation. Reported cases of lactic acidosis in patients on metformin hydrochloride have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing also other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia (see **CONTRAINDICATIONS**). Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Diagnosis

The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps with digestive disorders as abdominal pain and severe asthenia.

Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin hydrochloride should be discontinued and the patient should be hospitalised immediately (see **OVERDOSAGE**).

Renal function

As metformin hydrochloride is excreted by the kidney, serum creatinine levels should be determined before initiating treatment and regularly thereafter:

- at least annually in patients with normal renal function
- at least two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly subjects

Decreased renal function in elderly subjects is frequent and asymptomatic (see **Pharmacokinetics in special patient groups – Elderly**). Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug.

Administration of iodinated contrast agent

As the intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure, metformin hydrochloride should be discontinued prior to, or at the time of the test and not be reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see **INTERACTIONS WITH OTHER MEDICINES**).

Hypoxic States

Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction and other conditions characterised by hypoxaemia have been associated with lactic acidosis and may also cause pre-renal azotemia. If such events occur in patients receiving TRAJENTAMET therapy, the medication should be promptly discontinued.

Surgery

Metformin hydrochloride must be discontinued 48 hours before elective surgery with general, spinal or peridural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and only if normal renal function has been established.

Use with Insulin

The use of TRAJENTAMET in combination with insulin has not been adequately studied.

Effects on Fertility

No studies on the effect on human fertility have been conducted for TRAJENTAMET.

Linagliptin

No studies on the effect on human fertility have been conducted for linagliptin. No adverse effects on fertility were observed in male and female rats given linagliptin orally up to the highest dose of 240 mg/kg/day (yielding approximately 1000 times the plasma AUC obtained in patients at the maximum recommended human dose [MRHD] of 5 mg/day) prior to and throughout mating).

Metformin hydrochloride

Fertility of male or female rats was unaffected by metformin when administered at doses up to 600 mg/kg/day, which is approximately 2 times the maximum recommended human daily dose based on body surface area comparisons.

Use in Pregnancy (Category C)

There are no adequate and well-controlled studies in pregnant women with TRAJENTAMET or its individual components. No adverse effects on embryofetal development were observed in rats given linagliptin and metformin in combination at an oral dose of 1/200 mg/kg/day [linagliptin/metformin] during the period of organogenesis (resulting in exposure 1.5 times that for linagliptin and 3 times that for metformin at the maximum recommended human dose). At higher doses (yielding greater than 9 times the clinical AUC for metformin), the metformin component of the combination was associated with an increased incidence of fetal rib and scapula malformations.

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

When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with TRAJENTAMET but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of fetal malformations associated with abnormal blood glucose levels.

Use in Lactation

No studies in lactating animals have been performed with the combination of metformin and linagliptin. Non-clinical studies with the individual active substances have shown excretion of both metformin and linagliptin into milk in lactating rats. Metformin is excreted with milk in humans. It is not known whether linagliptin is excreted into human milk. TRAJENTAMET should not be used during breast-feeding.

Paediatric Use

Safety and effectiveness of TRAJENTAMET in paediatric patients under 18 years have not been established.

Use in the elderly

The risk of lactic acidosis, in association with metformin, is increased in elderly patients on long-term therapy due to the physiological alteration of the renal function and the possible accumulation of metformin. Metformin may be used in the elderly if Contraindications and Precautions are respected, the dosage is frequently reviewed and renal function monitored.

Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired.

Genotoxicity

Linagliptin

Linagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a chromosomal aberration test in human lymphocytes, and an *in vivo* micronucleus assay in the rat.

Metformin hydrochloride

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*Salmonella typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Carcinogenicity

Linagliptin

No evidence of carcinogenicity was observed with linagliptin in 2-year studies in mice and rats given oral doses up to 80 mg/kg/day and 60 mg/kg/day, respectively. These doses correspond to approximately 300 and 400 times the human exposure (plasma AUC) at the MRHD of 5 mg/day.

Metformin hydrochloride

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

INTERACTIONS WITH OTHER MEDICINES

General

Co-administration of multiple doses of linagliptin (10 mg once daily) and metformin (850 mg twice daily) did not meaningfully alter the pharmacokinetics of either linagliptin or metformin in healthy volunteers.

Pharmacokinetic drug interaction studies with TRAJENTAMET have not been performed; however, such studies have been conducted with the individual active substances of TRAJENTAMET: linagliptin and metformin.

Linagliptin

In vitro assessment of drug 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 inhibits P-glycoprotein mediated transport of digoxin with low potency. Based on these results and *in vivo* drug interaction studies, linagliptin is considered unlikely to cause interactions with other P-glycoprotein substrates. However, as linagliptin is a P-glycoprotein substrate, inhibitors/inducers of this transporter may affect linagliptin plasma kinetics.

In vivo assessment of drug interactions

Clinical data described below suggest that the risk for clinically meaningful interactions by co-administered medicinal products is low. No clinically significant interactions requiring dose adjustment were observed.

Linagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glibenclamide, simvastatin, pioglitazone, warfarin, digoxin or oral contraceptives providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-glycoprotein, and organic cationic transporter (OCT).

Metformin: Co-administration of multiple three-times-daily doses of 850 mg metformin with a supratherapeutic dose of 10 mg linagliptin once daily did not clinically meaningfully alter the pharmacokinetics of linagliptin or metformin in healthy volunteers. Therefore, linagliptin is not an inhibitor of OCT-mediated transport.

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

Thiazolidinediones: Co-administration of multiple daily doses of 10 mg linagliptin (supratherapeutic) with multiple daily doses of 45 mg pioglitazone, a CYP2C8 and CYP3A4 substrate, had no clinically relevant effect on the pharmacokinetics of either linagliptin or pioglitazone or the active metabolites of pioglitazone, indicating that linagliptin is not an inhibitor of CYP2C8-mediated metabolism *in vivo* and supporting the conclusion that the *in vivo* inhibition of CYP3A4 by linagliptin is negligible.

Ritonavir: A study was conducted to assess the effect of ritonavir, a potent inhibitor of P-glycoprotein and CYP3A4, on the pharmacokinetics of linagliptin. Co-administration of a single 5 mg oral dose of linagliptin and multiple 200 mg oral doses of ritonavir increased the AUC and C_{max} of linagliptin approximately twofold and threefold, respectively. 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 and dose adjustment is not required.

Rifampicin: A study was conducted to assess the effect of rifampicin, a potent inducer of P-glycoprotein and CYP3A4, on the pharmacokinetics of 5 mg linagliptin. Multiple co-administration of linagliptin with rifampicin, resulted in a 39.6% and 43.8% decreased linagliptin steady-state AUC and C_{max} and about 30% decreased DPP-4 inhibition at trough. Thus linagliptin in combination with strong P-glycoprotein inducers is expected to be clinically efficacious, although full efficacy might not be achieved.

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, showing that linagliptin is not an inhibitor of CYP2C9.

Simvastatin: Multiple daily doses of 10 mg linagliptin (supratherapeutic) had a minimal effect on the steady state pharmacokinetics of simvastatin, a sensitive CYP3A4 substrate, in healthy volunteers. Following administration 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%. Therefore, linagliptin is considered to be a weak inhibitor of CYP3A4-mediated metabolism, and dosage adjustment of concomitantly administered substances metabolised by CYP3A4 is considered unnecessary.

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

Metformin

There is increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic insufficiency) due to the metformin active substance of TRAJENTAMET (see **PRECAUTIONS – Lactic acidosis**). Consumption of alcohol and medicinal products containing alcohol should be avoided.

Glucocorticoids (given by systemic and local routes) beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment with such medicinal products. If necessary, the dose of the anti-hyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

ACE-inhibitors may decrease the blood glucose levels. If necessary, the dose of the antihyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

Cationic agents that are eliminated by renal tubular secretion (e.g., cimetidine) may interact with metformin by competing for common renal tubular transport systems. A study conducted in seven normal healthy volunteers showed that cimetidine, administered as 400 mg twice daily, increased metformin systemic exposure (AUC) by 50% and C_{max} by 81%. Therefore, close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic agents that are eliminated by renal tubular secretion are co-administered.

The intravascular administration of iodinated contrast agents in radiological studies may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. Therefore, TRAJENTAMET should be discontinued prior to, or at the time of the test and not reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal

(see **CONTRAINDICATIONS** and **PRECAUTIONS – Administration of iodinated contrast agent**).

ADVERSE EFFECTS

Adverse Reactions in Clinical Trials

Linagliptin/Metformin

The safety of linagliptin + metformin administered as single entity tablets has been evaluated in over 3000 patients with type 2 diabetes mellitus in clinical trials.

Three placebo-controlled studies with linagliptin + metformin were conducted, 2 investigated at least 24 weeks of treatment, 1 investigated at least 12 weeks of treatment. In the 3 placebo-controlled clinical studies, adverse events which occurred regardless of investigator assessment of causality in $\geq 5\%$ of patients receiving linagliptin + metformin (n = 875) and more commonly than in patients given placebo + metformin (n = 539) included nasopharyngitis (5.7% vs 4.3%); no adverse reactions were reported in 2% of patients treated with linagliptin and metformin and at least 2-fold greater than with placebo.

In a 24-week factorial design study, adverse events reported regardless of investigator assessment of causality in $\geq 5\%$ of patients treated with linagliptin + metformin and more commonly than in patients given placebo are shown in Table 2.

Table 2 Adverse Reactions (Irrespective of Investigator Assessment of Causality) Reported in 5% of Patients Treated with Linagliptin + Metformin and Greater than with Placebo in a 24-week Factorial-Design Study

	Placebo n = 72	Linagliptin Monotherapy n = 142	Metformin Monotherapy n = 291	Combination of Linagliptin with Metformin n = 286
	n (%)	n (%)	n (%)	n (%)
Nasopharyngitis	1 (1.4)	8 (5.6)	8 (2.7)	18 (6.3)
Diarrhoea	2 (2.8)	5 (3.5)	11 (3.8)	18 (6.3)

A further 24-week, placebo-controlled study with add-on treatment of linagliptin + metformin and a sulfonylurea was conducted. Adverse events which occurred regardless of investigator assessment of causality in $\geq 5\%$ of patients receiving linagliptin + metformin + sulfonylurea (n = 792) and more commonly than in patients given placebo (metformin + sulfonylurea) (n = 263) included nasopharyngitis (5.2% vs 4.6%) and hypoglycaemia (22.9% vs 14.8%).

Other adverse reactions reported in clinical studies with treatment of linagliptin + metformin were hypersensitivity (e.g., urticaria, angioedema, or bronchial hyperactivity), cough, decreased appetite, nausea, vomiting, and pruritus.

Linagliptin

One adverse reaction, nasopharyngitis, was reported in $\geq 5\%$ of patients treated with linagliptin and more commonly than in patients treated with placebo. In the clinical trial program, pancreatitis was reported in 8 of 4687 patients (4311 patient years of exposure) while being treated with linagliptin compared with 0 of 1183 patients (433 patient years of exposure) treated with placebo. Three additional cases of pancreatitis were reported following the last administered dose of linagliptin.

Other adverse reactions reported in clinical studies with treatment of linagliptin monotherapy were hypersensitivity (e.g., urticaria, angioedema, localized skin exfoliation, or bronchial hyperactivity), and cough.

Metformin hydrochloride

The following established adverse reactions of metformin are listed below by system organ class and frequency according to the following categories: Very common $\geq 10\%$, Common $\geq 1\%$ and $< 10\%$, Uncommon $\geq 0.1\%$ and $< 1\%$, Rare $\geq 0.01\%$ and $< 0.1\%$, Very rare $< 0.01\%$:

Gastrointestinal disorders¹

Very common: diarrhoea, nausea, vomiting, abdominal pain, decreased appetite

Hepatobiliary disorders

Very rare: liver function test abnormalities, hepatitis²

Metabolism and nutrition disorder

Very rare: decrease in vitamin B12 absorption³, lactic acidosis

Nervous system disorders

Common: taste disturbance

Skin and subcutaneous tissue disorders

Very rare: skin reactions such as erythema, pruritus and urticaria

¹ Gastrointestinal undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 daily doses during or after meals. A slow increase in the dose may also improve gastrointestinal tolerability.

² Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B12 deficiency (e.g., megaloblastic anaemia).

³ Isolated cases of liver function test abnormalities or hepatitis resolving upon metformin discontinuation have been reported.

Hypoglycaemia

In the placebo-controlled studies (linagliptin + metformin vs placebo + metformin), 7 (0.8%) of the total 875 patients treated with linagliptin + metformin reported hypoglycaemia which were all mild in intensity, compared to 11 (2.0%) reports of hypoglycemia with placebo + metformin of which 10 were mild and 1 was severe in intensity. When linagliptin was administered in combination with metformin and a sulfonylurea, 180 (22.7%) of 792 patients reported hypoglycaemia compared with 39 (14.8%) of 263 patients administered placebo in combination with metformin and sulfonylurea.

Laboratory Tests

Changes in laboratory findings were similar in patients treated with linagliptin + metformin compared to patients treated with placebo + metformin. Changes in laboratory values that occurred more frequently in the linagliptin + metformin group and 1% more than in the placebo group were not detected.

No clinically meaningful changes in vital signs were observed in patients treated with linagliptin.

Post marketing experience

From post-marketing experience, the following side effects have been reported and are listed below by system organ class and frequency according to the following categories:

Common $\geq 1\%$ and $< 10\%$, Uncommon $\geq 0.1\%$ and $< 1\%$, Rare $\geq 0.01\%$ and $< 0.1\%$

Linagliptin

From post-marketing experience with linagliptin, the following side effects have been reported:

Immune system disorders

Rare: angioedema, urticaria

Skin and subcutaneous tissue disorders

Uncommon: rash

DOSAGE AND ADMINISTRATION

Life-threatening lactic acidosis can occur due to accumulation of metformin. Risk factors include renal impairment, old age and the use of high doses of metformin above 2000 mg per day.

TRAJENTAMET is available in three strengths:

TRAJENTAMET 2.5 mg/500 mg containing 2.5 mg linagliptin with 500 mg metformin hydrochloride

TRAJENTAMET 2.5 mg/850 mg containing 2.5 mg linagliptin with 850 mg metformin hydrochloride

TRAJENTAMET 2.5 mg/1000 mg containing 2.5 mg linagliptin with 1000 mg metformin hydrochloride

The recommended dose is TRAJENTAMET 2.5 mg/500 mg, 2.5 mg/850 mg or 2.5 mg/1000 mg twice daily.

The dosage should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability. Maximum recommended daily dose of TRAJENTAMET is 5 mg of linagliptin and 2000 mg of metformin.

TRAJENTAMET should be given with meals to reduce the gastrointestinal undesirable effects associated with metformin.

For patients inadequately controlled on maximal tolerated dose of metformin monotherapy

For patients not adequately controlled on metformin alone, the usual starting dose of TRAJENTAMET should provide linagliptin dosed as 2.5 mg twice daily (5 mg total daily dose) plus the dose of metformin already being taken.

For patients switching from co-administration of linagliptin and metformin

For patients switching from co-administration of linagliptin and metformin to the fixed dose combination, TRAJENTAMET should be initiated at the dose of linagliptin and metformin already being taken.

For patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a sulfonylurea

The dose of TRAJENTAMET should provide linagliptin dosed as 2.5 mg twice daily (5 mg total daily dose) and a dose of metformin similar to the dose already being taken. When TRAJENTAMET is used in combination with a sulfonylurea, a lower dose of the sulfonylurea may be required to reduce the risk of hypoglycaemia (see **PRECAUTIONS**).

Renal impairment

TRAJENTAMET is contraindicated in patients with moderate or severe renal dysfunction (creatinine clearance < 60 mL/min) due to the metformin component (see **CONTRAINDICATIONS**).

Hepatic impairment

TRAJENTAMET is contraindicated in patients with hepatic insufficiency due to the metformin component (see **CONTRAINDICATIONS**).

Elderly

As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking TRAJENTAMET should have their renal function monitored regularly (see **PRECAUTIONS**).

Children and adolescents

TRAJENTAMET is not recommended for use in children below 18 years due to lack of data on safety and efficacy.

OVERDOSAGE

In case of overdose, advice can be obtained from the Poisons Information Centre (telephone 13 11 26).

Symptoms

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

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin hydrochloride or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital.

Therapy

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring and institute clinical measures as required. The most effective method to remove lactate and metformin hydrochloride is haemodialysis.

PRESENTATION AND STORAGE CONDITIONS

TRAJENTAMET is available in three strengths:

TRAJENTAMET 2.5 mg/500 mg - oval, biconvex, light yellow, one side debossed with the Boehringer Ingelheim company symbol, the other side debossed with 'D2/500'.

TRAJENTAMET 2.5 mg/850 mg - oval, biconvex, light orange, one side debossed with the Boehringer Ingelheim company symbol, the other side debossed with 'D2/850'.

TRAJENTAMET 2.5 mg/1000 mg - oval, biconvex, light pink, one side debossed with the Boehringer Ingelheim company symbol, the other side debossed with 'D2/1000'

TRAJENTAMET is available in blister packs containing 10*, 14, 28*, 30*, 56*, 60, 84*, 90* 98*, 100*, 120* tablets; and in HDPE bottles containing 14*, 60* and 180* film-coated tablets.

**not currently distributed in Australia*

Store below 30°C. Protect from moisture.

NAME AND ADDRESS OF THE SPONSOR

Boehringer Ingelheim Pty Limited

ABN 52 000 452 308

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POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG): 21 MAY 2013