

AUSTRALIAN PRODUCT INFORMATION – TRAJENTAMET (linagliptin/metformin hydrochloride) film-coated tablet

1 NAME OF THE MEDICINE

linagliptin and metformin hydrochloride.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TRAJENTAMET contains two oral antihyperglycaemic drugs used in the management of type 2 diabetes mellitus (T2DM): linagliptin (a dipeptidyl peptidase-4 (DPP-4) inhibitor) and metformin hydrochloride.

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.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

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'

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

TRAJENTAMET is indicated in combination with an SGLT2 inhibitor (i.e. triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximum tolerated dose of metformin and an SGLT2 inhibitor.

TRAJENTAMET is indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when insulin and metformin alone do not provide adequate glycaemic control.

4.2 DOSE AND METHOD OF 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

Adults with normal renal function (GFR \geq 90mL/min)

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 (see table 1 for additional dosing information).

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

For patients currently not treated with metformin

For patients currently not treated with metformin, the recommended starting dose is TRAJENTAMET 2.5 mg linagliptin/500 mg metformin hydrochloride twice daily.

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 Section 4.4 Special Warnings and Precautions for Use).

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

The dose of TRAJENTAMET 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 insulin, a lower dose of insulin may be required to reduce the risk of hypoglycaemia (see Section 4.4 Special Warnings and Precautions for Use).

Renal impairment

TRAJENTAMET is contraindicated in patients with severe renal failure (creatinine clearance $<$ 30 mL/min or eGFR $<$ 30 mL/min/1.73m²) due to the metformin component (see Section 4.3 Contraindications).

Renal function should be assessed before initiation of treatment with metformin containing products and at least annually thereafter.

In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months (see Section 4.4 Special Warnings and Precautions for Use).

Factors that may increase the risk of lactic acidosis (see Section 4.4 Special Warning and Precautions for Use) should be reviewed before considering initiation of metformin in patients with GFR < 60 mL/min.

Table 1 Dosage for renally impaired patients*

eGFR mL/min	Metformin	Linagliptin
60 - 89	Maximum daily dose is 3000 mg*. Dose reduction may be considered in relation to declining renal function.	No dose adjustment is required.
45 - 59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	No dose adjustment is required.
30 - 44	Maximum daily dose is 1000 mg*. The starting dose is at most half of the maximum dose.	No dose adjustment is required.
< 30	Metformin is contraindicated.	No dose adjustment is required.

*If no adequate strength of TRAJENTAMET is available, individual monocomponents should be used instead of the fixed dose combination.

Hepatic impairment

TRAJENTAMET is contraindicated in patients with hepatic impairment due to the metformin component (see Section 4.3 Contraindications).

Elderly

As metformin is excreted via the kidney, and elderly patients have a tendency for decreased renal function, elderly patients taking TRAJENTAMET should have their renal function monitored regularly (see Section 4.4 Special Warnings and Precautions for Use).

Children and adolescents

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

4.3 CONTRAINDICATIONS

- Hypersensitivity to active ingredients linagliptin and/or metformin hydrochloride or to any of the excipients
- Any type of metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma
- Severe renal failure (creatinine clearance < 30 mL/min or eGFR < 30 mL/min/1.73m²), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicaemia
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock, intravascular administration of iodinated contrast agents (see Section 4.4 Special Warnings and Precautions for Use)
- Acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, recent myocardial infarction, shock, pulmonary embolism, acute significant blood loss, sepsis, gangrene, pancreatitis (see Section 4.4 Special Warnings and Precautions for Use)
- During or immediately following surgery where insulin is essential, elective major surgery

- Hepatic impairment, acute alcohol intoxication, alcoholism (due to the metformin component)
- Lactation

TRAJENTAMET must 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 Section 4.4 Special Warnings and Precautions for Use - Administration of iodinated contrast agent).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

TRAJENTAMET should not be used in patients with type 1 diabetes.

Pancreatitis

Acute pancreatitis has been observed 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 and insulin are known to cause hypoglycaemia. Therefore, caution is advised when TRAJENTAMET is used in combination with a sulfonylurea and/or with insulin. A dose reduction of the sulfonylurea or insulin 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, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients.

Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see also Sections 4.3 Contraindications and 4.5 Interactions with Other Medicines and Other Forms of Interactions).

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and be hospitalised immediately.

Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (>5 mmol/L), and an increased anion gap and lactate/pyruvate ratio.

Administration of iodinated contrast agent

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be

discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see Sections 4.2 Dose and Method of Administration and 4.5 Interactions with Other Medicines and Other Forms of Interactions.

Surgery

Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Bullous pemphigoid

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

Arthralgia

There have been postmarketing reports of joint pain, which may be severe, in patients taking DPP-4 inhibitors. Onset of symptoms following initiation of treatment may be rapid or may occur after longer periods. Discontinuation of therapy should be considered in patients who present with or experience an exacerbation of joint symptoms during treatment with linagliptin.

Vitamin B12 levels

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B12 supplementation. Measurement of haematologic parameters on an annual basis is advised in patients on TRAJENTAMET and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate Vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B12 levels. In these patients, routine serum Vitamin B12 measurements at two- to three-year intervals may be useful.

Immunocompromised patients

Immunocompromised patients, such as patients who have undergone organ transplantation or patients diagnosed with human immunodeficiency syndrome, have not been studied in the linagliptin clinical program. Therefore, the efficacy and safety profile of linagliptin in these patients has not been established.

Combination with glucagon like peptide (GLP-1) analogues

Linagliptin has not been studied in combination with glucagon like peptide 1 (GLP-1) analogues.

Use in renal impairment

GFR should be assessed before treatment initiation and regularly thereafter, see section 4.2 Dose and Method of Administration. TRAJENTAMET is contraindicated in patients with GFR < 30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function, see section 4.3 Contraindications.

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.

Paediatric Use

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

Effects on laboratory tests

See Section 4.8 Adverse Effects (Undesirable Effects), Laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pharmacokinetic Interactions

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 was 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

Contraindicated combinations

Iodinated contrast materials

TRAJENTAMET must be discontinued prior to, or at the time of the imaging procedure and not be restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see Section 4.3 Contraindications and Section 4.4 Special Warnings and Precautions for Use - Administration of iodinated contrast materials).

Inadvisable combinations

Alcohol

There is increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic impairment) due to the metformin component of TRAJENTAMET (see Section 4.4 Special Warnings and Precautions for Use – Lactic acidosis). Consumption of alcohol and medicinal products containing alcohol should be avoided. Alcohol may make the signs of hypoglycaemia less clear, and delayed hypoglycaemia can occur. The CNS depressant effects of alcohol plus hypoglycaemia can make driving or the operation of dangerous machinery much more hazardous.

Combinations requiring precautions for use

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Medicinal products with intrinsic hyperglycaemic activity e.g. glucocorticoids and tetracosactides (systemic and local routes), beta-2-agonists, danazol, chlorpromazine at high dosages of 100 mg per day and diuretics

More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon discontinuation.

Diuretics, especially loop diuretics

May increase the risk of lactic acidosis due to their potential to decrease renal function.

ACE-inhibitors

ACE-inhibitors may decrease the blood glucose levels. Therefore, dose adjustment of TRAJENTAMET may be necessary when such medicinal products are added or discontinued.

Calcium channel blockers

Calcium channel blockers may affect glucose control in diabetic patients; regular monitoring of glycaemic control is recommended.

Beta-blockers

Co-administration of metformin and beta-blockers may result in a potentiation of the anti-hyperglycaemic action. In addition, some of the premonitory signs of hypoglycaemia, in particular tachycardia, may be masked. Monitoring of blood glucose should be undertaken during dosage adjustment of either agent.

Cimetidine

Reduced clearance of metformin has been reported during cimetidine therapy, so a dose reduction should be considered.

Anticoagulants

Metformin increases the elimination rate of vitamin K antagonists. Consequently, the prothrombin time should be closely monitored in patients in whom metformin and vitamin K antagonists are being co-administered. Cessation of metformin in patients receiving vitamin K antagonists can cause marked increases in the prothrombin time.

Nifedipine

A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of metformin and nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount of metformin excreted in the urine. T_{max} and half-life of metformin were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on the pharmacokinetics of nifedipine.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of metformin with:

- Substrates/inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Substrates/inhibitors of OCT2 (such as cimetidine, dolutegravir, crizotinib, olaparib, daclatasvir, vandetanib) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.

Carbonic anhydrase inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with metformin hydrochloride tablet may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients.

NSAID

May increase the risk of lactic acidosis and adversely affect renal function.

Therefore, caution is advised when these drugs are co-administered with metformin and a dose adjustment may be considered, particularly in patients with renal impairment.

4.6 FERTILITY, PREGNANCY AND LACTATION

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 into human breast milk. It is not known whether linagliptin is excreted into human milk. TRAJENTAMET should not be used during breast-feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

Low blood sugar may occur in patients who already take another medication to treat diabetes such as a sulfonylurea or insulin while taking TRAJENTAMET. The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance e.g. driving a car or operating machinery. People should be advised to take precautions to avoid hypoglycaemia whilst driving or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

Adverse Reactions in Clinical Trials

Linagliptin/Metformin

The safety of linagliptin + metformin has been evaluated in over 6800 patients with T2DM 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 (AEs) 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, AEs 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. AEs 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%).

Adverse reactions reported with the fixed dose combination

Adverse reactions reported in all clinical trials with TRAJENTAMET are shown below according to system organ class. Adverse reactions known to occur with each active substance given singly, but which have not been seen in clinical trials with TRAJENTAMET, may occur during treatment with this medicinal product.

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

Table 3 Adverse reactions reported in patients who received TRAJENTAMET (frequencies identified from pooled analysis of placebo-controlled studies) in clinical trials

System organ class Adverse reaction	linagliptin + metformin
Infections and infestations	
Nasopharyngitis	uncommon
Immune system disorders	
Hypersensitivity (e.g. bronchial hyperreactivity)	uncommon
Respiratory, thoracic and mediastinal disorders	
Cough	uncommon
Gastrointestinal disorders	
Decreased appetite	uncommon
Diarrhoea	common
Nausea	uncommon
Pancreatitis	rare
Vomiting	uncommon
Skin and subcutaneous tissue disorders	
Pruritus	uncommon
Investigations	
Lipase increased ¹	Common
Amylase increased*	Uncommon

¹ based on lipase elevations >3xULN observed in clinical trials

* In the CAROLINA study comparing linagliptin with active comparator glimepiride (see Section 5.1 Pharmacodynamic properties, Clinical Trials) laboratory analysis of amylase showed increases to >3 x ULN in 0.99% of patients treated with linagliptin and in 0.54% of patients treated with glimepiride.

Adverse reactions reported when linagliptin and metformin were combined with sulfonylurea

When linagliptin and metformin were administered in combination with a sulfonylurea, hypoglycaemia was identified as an additional adverse reaction under these conditions (Table 4). None of the hypoglycaemias was classified as severe (requiring assistance).

Table 4 Adverse reactions additionally reported in patients when linagliptin and metformin were combined with sulfonylurea

System organ class Adverse reaction	linagliptin + metformin + sulfonylurea
Metabolism and nutrition disorders	
Hypoglycaemia	very common

Adverse reactions reported when linagliptin and metformin were combined with empagliflozin

When linagliptin and metformin were administered in combination with empagliflozin, no additional adverse reactions were identified.

Adverse reactions reported when linagliptin and metformin were combined with insulin

When linagliptin and metformin were administered in combination with insulin, constipation was identified as an additional adverse reaction under these conditions (Table 5).

Table 5 Adverse reactions additionally reported in patients when linagliptin and metformin were combined with insulin

System organ class Adverse reaction	linagliptin + metformin + insulin
Gastrointestinal disorders	
Constipation	uncommon

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 $< 0.01\%$.

System Organ Class Adverse reaction	Metformin hydrochloride monotherapy
Gastrointestinal disorders¹	
Abdominal pain	very common
Decreased appetite	very common
Diarrhoea	very common
Nausea	very common
Vomiting	very common
Hepatobiliary disorders²	
Hepatitis	very rare
Liver function test abnormalities	very rare
Metabolism and nutrition disorder	
Decrease in vitamin B12 absorption ³	very rare
Lactic acidosis	very rare
Nervous system disorders	
Taste disturbance	common
Skin and subcutaneous tissue disorders	
Skin reactions such as erythema, pruritus and urticaria	very rare

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 metformin dose may also improve gastrointestinal tolerability.

² Isolated cases of liver function test abnormalities or hepatitis resolving upon metformin discontinuation have been reported.

³ Decrease of vitamin B12 absorption with a decrease in serum levels has been observed in patients treated long-term with metformin. Consideration of such an aetiology is recommended if a patient presents with megaloblastic anaemia. Therefore, serum B12 levels should be appropriately monitored or periodic parenteral B12 supplementation should be considered (see Section 4.4 Special Warnings and Precautions for Use – Vitamin B12 levels).

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 hypoglycaemia 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.

When linagliptin and metformin were administered in combination with insulin, hypoglycaemia was the most commonly reported adverse event, but occurred at comparable rate when placebo and metformin were combined with insulin (linagliptin plus metformin plus insulin 29.5% vs 30.9% in the placebo plus metformin plus insulin group) with a low rate of severe (requiring assistance) episodes (1.5% vs. 0.9%).

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.

Postmarketing experience

From postmarketing experience, the following adverse reactions 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 $< 0.1\%$, Very rare ($< 0.01\%$), not known (cannot be estimated from the available data).

Linagliptin

From postmarketing experience with linagliptin, the following adverse reactions have been reported:

System Organ Class Adverse reaction	Linagliptin
Immune system disorders	
Angioedema	rare
Urticaria	rare
Skin and subcutaneous tissue disorders	
Rash	uncommon
Bullous pemphigoid	rare*
Gastrointestinal disorders	
Mouth ulceration	rare

System Organ Class	Linagliptin
Adverse reaction	
Musculoskeletal and connective tissue disorders	
Arthralgia	rare
Myalgia	rare
Rhabdomyolysis	rare

*See also Linagliptin cardiovascular and renal safety study (CARMELINA) below

Linagliptin cardiovascular outcome and renal safety study (CARMELINA)

The CARMELINA study evaluated the cardiovascular and renal safety of linagliptin versus placebo in patients with type 2 diabetes and with increased CV risk evidenced by a history of established macrovascular or renal disease (see section 5.1 Pharmacodynamic Properties, Clinical Trials). The study included 3,494 patients treated with linagliptin (5 mg) and 3,485 patients treated with placebo. Both treatments were added to standard of care targeting regional standards for HbA1c and CV risk factors; with 54% on metformin. The overall incidence of adverse events and serious adverse events in patients receiving linagliptin was similar to that in patients receiving placebo. Safety data from this study was in line with previous known safety profile of linagliptin.

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

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

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

4.9 OVERDOSE

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Mechanism of action

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.

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 6 (mean baseline HbA1c 8.65%).

Table 6 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 FPG with -0.7 mmol/L reduction compared to placebo. Body weight did not differ significantly between the groups.

Linagliptin as add-on to a combination of metformin and empagliflozin

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 -0.25, -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 $\geq 7.0\%$ and treated with linagliptin 5 mg achieved a target HbA1c of $< 7\%$ compared to placebo.

In prespecified subgroups of patients with baseline HbA1c greater or equal than 8.5% (n=66 and n=42 patients on metformin plus empagliflozin 10 mg or 25 mg, respectively), the adjusted mean HbA1c reductions from baseline to 24 weeks on add-on therapy with linagliptin 5 mg were -0.97% (p=0.0875, for difference to add-on placebo) and -1.16% (p=0.0046 for difference to add-on placebo), respectively.

Linagliptin in combination with metformin and insulin

A 24-week placebo-controlled study was conducted to evaluate the efficacy and safety of linagliptin (5 mg once daily) added to insulin with or without metformin. 83% of patients were taking metformin in combination with insulin in this trial. Linagliptin in combination with metformin plus insulin provided significant improvements in HbA1c in this subgroup with -0.68% (CI: -0.78; -0.57) adjusted mean change from baseline (mean baseline HbA1c 8.28%) compared to placebo in combination with metformin plus insulin. There was no meaningful change from baseline in body weight in either group.

Linagliptin in combination with metformin and insulin - Use in elderly patients (age ≥ 70 years) with type 2 diabetes

In a pooled analysis of elderly (age ≥ 70 years) patients with type 2 diabetes (n=183) who were taking both metformin and basal insulin as background therapy, linagliptin in combination with metformin plus insulin provided significant improvements in HbA1c parameters with -0.81% (CI: -1.01, -0.61) adjusted mean change from baseline (mean baseline HbA1c 8.13%) compared to placebo in combination with metformin plus insulin. There was no clinically meaningful difference in the

incidence of hypoglycaemic events, in patients ≥ 70 years (37.2% on linagliptin in combination with metformin plus insulin vs. 39.8% on placebo in combination with metformin plus insulin).

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 sulfonyleurea 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).

Linagliptin as add on therapy in elderly patients (age ≥ 70 years) with type 2 diabetes

The efficacy and safety of linagliptin in elderly (age ≥ 70 years) type 2 diabetes patients was evaluated in a double blind study of 24 weeks duration. Patients received metformin and/or sulfonyleurea and/or insulin as background therapy. Doses of background antidiabetic medications were kept stable during the first 12 weeks, after which adjustments were permitted. Linagliptin provided significant improvements in HbA1c of -0.64% (95% CI -0.81, -0.48; $p < 0.0001$) compared to placebo after 24 weeks, from a mean baseline HbA1c of 7.8%. Linagliptin also showed significant improvements in FPG of -1.1 mmol/L (95% CI -1.7, -0.6; $p < 0.0001$) compared to placebo. Body weight did not differ significantly between the groups. Overall, the incidence of hypoglycaemia was comparable between linagliptin (2 of 45 patients, 4.4%) and placebo (none of 22 patients, 0%) on the background of metformin alone. Hypoglycaemia rates were also comparable on a background of insulin with or without metformin (linagliptin: 13 of 35 patients, 37.1%, placebo: 6 of 15 patients, 40.0%). However, on a background of sulfonyleurea with or without metformin, hypoglycaemia was reported in a higher proportion of patients treated with linagliptin (24 of 82 patients, 29.3%) compared to placebo (7 of 42 patients, 16.7%). There was no difference between linagliptin and placebo in severe hypoglycaemic events.

Linagliptin cardiovascular and renal safety study (CARMELINA)

CARMELINA was a randomised study in 6,979 patients with type 2 diabetes with increased CV risk evidenced by a history of established macrovascular or renal disease who were treated with linagliptin 5 mg (3,494) or placebo (3,485) added to standard of care targeting regional standards for HbA1c, CV risk factors and renal disease. The study population included 1,211 (17.4%) patients ≥ 75 years of age and 4,348 (62.3%) patients with renal impairment. Approximately 19% of the population had eGFR ≥ 45 to < 60 mL/min/1.73 m², 28% of the population had eGFR ≥ 30 to < 45 mL/min/1.73 m² and 15% had eGFR < 30 mL/min/1.73 m².

The mean HbA1c at baseline was 8.0%.

The study was designed to demonstrate non-inferiority for the primary cardiovascular endpoint which was a composite of the first occurrence of cardiovascular death or a non-fatal myocardial infarction (MI) or a non-fatal stroke (3P-MACE). The renal composite endpoint was defined as renal death or sustained end stage renal disease or sustained decrease of 40% or more in eGFR.

The median follow-up was for 2.2 years. When added to the standard of care, linagliptin was shown to be non-inferior to placebo with regard to the risk of occurrence of the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (Table 7 and Figure 1).

For the key secondary renal endpoint, which was time to the first occurrence of renal death, sustained end stage renal disease (ESRD), or sustained decrease of 40% or more in eGFR from baseline, linagliptin was not superior to placebo (HR: 1.04; 95% CI: 0.89, 1.22) (Table 7).

The risk of the composite endpoints hospitalisation for heart failure or cardiovascular death, and hospitalisation for heart failure and all-cause mortality was also balanced across the treatment groups (Table 8).

Table 7 Major adverse cardiovascular events (MACE) and renal outcome events by treatment group in the CARMELINA study

	Linagliptin 5mg		Placebo		Hazard Ratio (95% CI)
	Number of Subjects (%)	Incidence Rate per 1000 PY*	Number of Subjects (%)	Incidence Rate per 1000 PY*	
Number of patients	3,494		3,485		
Primary CV composite (Cardiovascular death, non-fatal MI, non-fatal stroke)	434 (12.4)	57.7	420 (12.1)	56.3	1.02 (0.89, 1.17)**
Secondary renal composite (renal death, ESRD, 40% sustained decrease in eGFR)	327 (9.4)	48.9	306 (8.8)	46.6	1.04 (0.89, 1.22)

* PY=patient years

** Test on non-inferiority to demonstrate that the upper bound of the 95% CI for the hazard ratio is less than 1.3

Figure 1 Time to first occurrence of 3P-MACE in CARMELINA

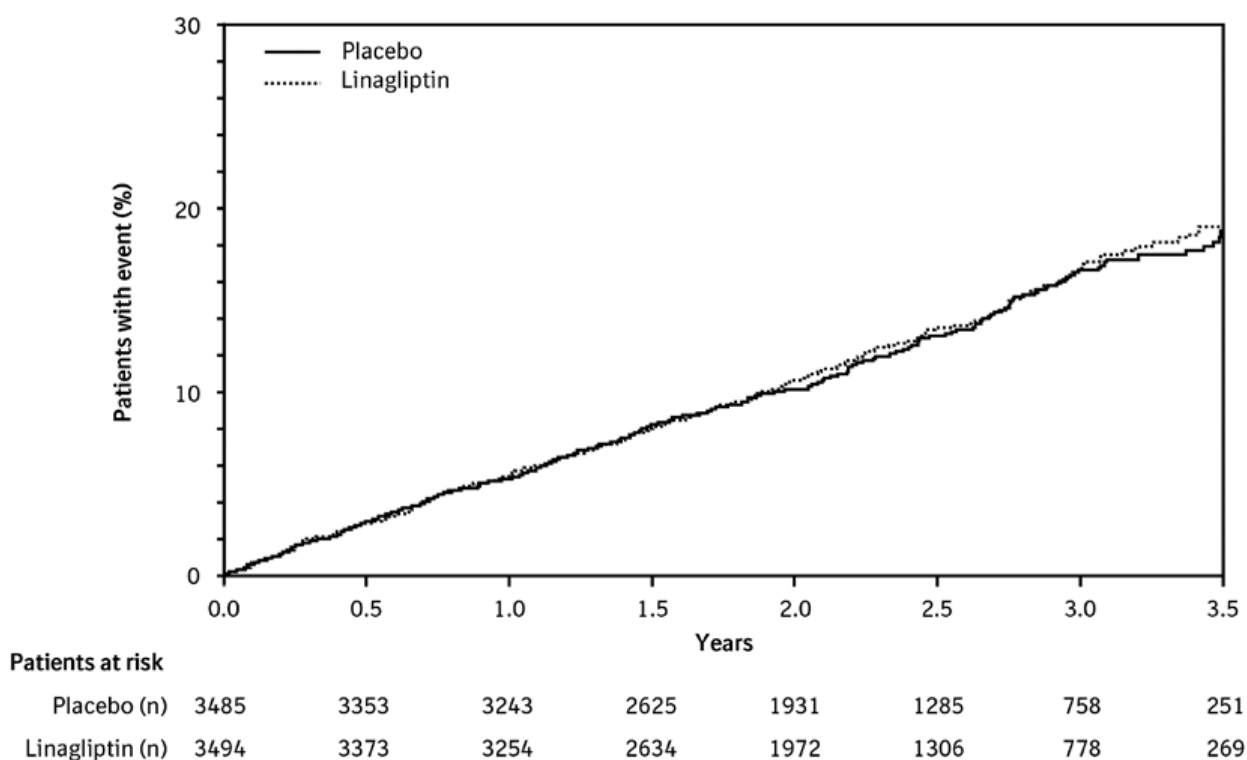


Table 8 Hospitalisation for heart failure and mortality by treatment group in the CARMELINA study

	Linagliptin 5mg		Placebo		Hazard Ratio (95% CI)
	Number of Subjects (%)	Incidence Rate per 1000 PY*	Number of Subjects (%)	Incidence Rate per 1000 PY*	
Number of patients	3,494		3,485		
All-cause mortality	367 (10.5)	46.9	373 (10.7)	48.0	0.98 (0.84, 1.13)
CV death	255 (7.3)	32.6	264 (7.6)	34	0.96 (0.81, 1.14)
Hospitalisation for heart failure	209 (6.0)	27.7	226 (6.5)	30.4	0.90 (0.74, 1.08)

* PY=patient years

Linagliptin cardiovascular safety study (CAROLINA)

CAROLINA was a randomised study in 6033 patients with early type 2 diabetes and increased CV risk or established complications who were treated with linagliptin 5 mg (3023) or glimepiride 1-4 mg (3010) added to standard of care (including background therapy with metformin in 83% of patients) targeting regional standards for HbA1c and CV risk factors. The mean age for study population was 64 years and included 2030 (34%) patients \geq 70 years of age. The study population included 2089 (35%) patients with cardiovascular disease and 1130 (19%) patients with renal impairment with an eGFR $<$ 60mL/min/1.73m² at baseline. The mean HbA1c at baseline was 7.15%.

The study was designed to demonstrate non-inferiority for the primary cardiovascular endpoint which was a composite of the first occurrence of cardiovascular death or a non-fatal myocardial infarction (MI) or a non-fatal stroke (3P-MACE).

After a median follow up of 6.25 years, linagliptin, when added to standard of care, did not increase the risk of major adverse cardiovascular events (Table 9) as compared to glimepiride. Results were consistent for patients treated with or without metformin.

Table 9 Major adverse cardiovascular events (MACE) and mortality by treatment group in the CAROLINA study

	Linagliptin 5mg		Glimepiride (1-4mg)		Hazard Ratio (95% CI)
	Number of Subjects (%)	Incidence Rate per 1000 PY*	Number of Subjects (%)	Incidence Rate per 1000 PY*	
Number of patients	3023		3010		
Primary CV composite (Cardiovascular death, non-fatal MI, non-fatal stroke)	356 (11.8)	20.7	362 (12.0)	21.2	0.98 (0.84, 1.14)**

* PY=patient years

** Test on non-inferiority to demonstrate that the upper bound of the 95% CI for the hazard ratio is less than 1.3

For the entire treatment period (median time on treatment 5.9 years) the rate of patients with moderate or severe hypoglycaemia was 6.5% on linagliptin versus 30.9% on glimepiride, severe hypoglycaemia occurred in 0.3% of patients on linagliptin versus 2.2% on glimepiride.

5.2 PHARMACOKINETIC PROPERTIES

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 [¹⁴C] 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.

Excretion

Following administration of an oral [¹⁴C]-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 is 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.

Excretion

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 antihyperglycaemic 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 impairment compared to normal healthy control subjects. The study included patients with renal impairment 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 T2DM and severe renal impairment (< 30 mL/min) were compared to patients with T2DM 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 T2DM and severe renal impairment was increased by about 1.4 fold compared to patients with T2DM 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 impairment. In addition, mild renal impairment had no effect on linagliptin pharmacokinetics in patients with T2DM 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 impairment

Linagliptin

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

Metformin hydrochloride

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

5.3 PRECLINICAL SAFETY DATA

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each film-coated tablet of TRAJENTAMET contains the following inactive ingredients: arginine, maize starch, copovidone, colloidal anhydrous silica, magnesium stearate, titanium dioxide, propylene glycol, hypromellose, purified talc, 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).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

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.*

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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: $\text{Log } P = 1.7$ (free base); $\text{Log } D$ (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.

Chemical structure

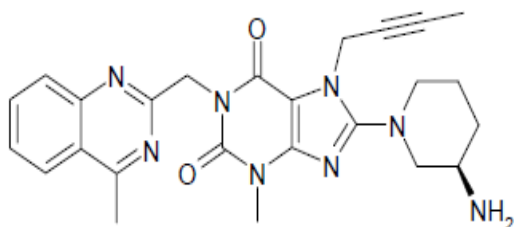
Linagliptin

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: $C_{25}H_{28}N_8O_2$

Molecular weight: 472.54

Structural formula:



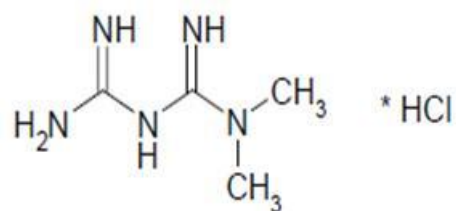
Metformin hydrochloride

Chemical name: 1,1-dimethylbiguanide hydrochloride

Molecular formula: $C_4H_{11}N_5.HCl$

Molecular weight: 165.63

Structural formula:



CAS number

Linagliptin: 668270-12-0

Metformin hydrochloride: 1115-70-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

21 May 2013

10 DATE OF REVISION

13 August 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Pancreatitis and bullous pemphigoid frequencies updated