Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Jentadueto 2.5 mg/850 mg film-coated tablets Jentadueto 2.5 mg/ 500 mg film-coated tablets Jentadueto 2.5 mg/1000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

- Jentadueto 2.5 mg/500 mg contains 2.5 mg linagliptin and 500 mg metformin hydrochloride
- Jentadueto 2.5 mg/850 mg contains 2.5 mg linagliptin and 850 mg metformin hydrochloride
- Jentadueto 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.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Jentadueto 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'.

Jentadueto 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'.

Jentadueto 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

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

- in patients inadequately controlled on their maximally tolerated dose of metformin alone
- in combination with other medicinal products for the treatment of diabetes, including insulin, in patients inadequately controlled with metformin and these medicinal products

- in patients already being treated with the combination of linagliptin and metformin as separate tablets.

(see sections 4.4, 4.5 and 5.1 for available data on different combinations).

4.2 Posology and method of administration

Posology

Adults with normal renal function (GFR ≥90 ml/ min)

The dose of antihyperglycaemic therapy with Jentadueto should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability, while not exceeding the maximum recommended daily dose of 5 mg linagliptin plus 2,000 mg of metformin hydrochloride.

Patients inadequately controlled on maximal tolerated dose of metformin monotherapy

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

Patients switching from co-administration of linagliptin and metformin

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

Patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a sulphonylurea

The dose of Jentadueto 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 linagliptin plus metformin hydrochloride is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be required to reduce the risk of hypoglycaemia (see section 4.4).

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

The dose of Jentadueto 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 linagliptin plus metformin hydrochloride is used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycaemia (see section 4.4).

For the different doses of metformin, Jentadueto is available in strengths of 2.5 mg linagliptin plus 850 mg metformin hydrochloride and 2.5 mg linagliptin plus 1,000 mg metformin hydrochloride.

Special populations

Elderly

As metformin is excreted by the kidney, Jentadueto should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly (see sections 4.3 and 4.4).

Renal impairment
An eGFR 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
eGFR< 60 mL/min.

Table 1: Posology for renally impaired patients

GFR 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
45-59	Maximum daily dose is 2000 mg The starting dose is at most half of the maximum dose.	No dose adjustment
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	No dose adjustment
<30	Metformin is contraindicated	No dose adjustment

Hepatic impairment
Jentadueto is not recommended in patients with hepatic impairment due to the active substance metformin (see sections 4.3 and 5.2). Clinical experience with Jentadueto in patients with hepatic impairment is lacking.

Children and adolescents
Jentadueto is not recommended for use in children below 18 years of age. See Section 4.4 Special warnings and precautions for use.

Method of administration
Jentadueto should be taken twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin.
All patients should continue their diet with an adequate distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.

If a dose is missed, it should be taken as soon as the patient remembers. However, a double dose should not be taken at the same time. In that case,

the missed dose should be skipped.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma.
- Severe renal failure (GFR <30 ml/min).
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock.
- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock.
- Hepatic impairment, acute alcohol intoxication, alcoholism (see section 4.5).

4.4 Special warnings and precautions for use

General
Jentadueto should not be used in patients with type 1 diabetes.

Hypoglycaemia
When linagliptin was added to a sulphonylurea on a background of metformin, the incidence of hypoglycaemia was increased over that of placebo.

Sulphonylureas and insulin are known to cause hypoglycaemia. Therefore, caution is advised when Jentadueto is used in combination with a sulphonylurea and/or insulin. A dose reduction of the sulphonylurea or insulin may be considered (see section 4.2).

Hypoglycaemia is not identified as adverse reaction for linagliptin, metformin, or linagliptin plus metformin. In clinical trials, the incidence rates of hypoglycemia were comparably low in patients taking linagliptin in combination with metformin or metformin alone.

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 impairment, 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 sections 4.3 and 4.5).

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. 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 and 4.5.

Renal function
GFR should be assessed before treatment initiation and regularly thereafter, see section 4.2. Metformin 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).

Cardiac function
Patients with heart failure are more at risk of hypoxia and renal impairment. In patients with stable chronic heart failure, Jentadueto may be used with a regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, Jentadueto is contraindicated (see section 4.3).

Surgery
Metformin must be discontinued at the time of surgery under general, spinal or epidural anesthesia. 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.

Elderly
Caution should be exercised when treating patients 80 years and older (see section 4.2).

Change in clinical status of patients with previously controlled type 2 diabetes
As Jentadueto contains metformin, a patient with previously well controlled type 2 diabetes on Jentadueto who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis.
Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, Jentadueto must be stopped immediately and

other appropriate corrective measures initiated.

Acute pancreatitis
Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Acute pancreatitis has been observed in patients taking linagliptin. In a cardiovascular and renal safety study (CARMELINA) with median observation period of 2.2 years, adjudicated acute pancreatitis was reported in 0.3% of patients treated with linagliptin and in 0.1% of patients treated with placebo.
Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Jentadueto should be discontinued; if acute pancreatitis is confirmed, Jentadueto should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Bullous pemphigoid
Bullous pemphigoid has been observed in patients taking linagliptin. In the CARMELINA study, bullous pemphigoid was reported in 0.2% of patients on treatment with linagliptin and in no patient on placebo. If bullous pemphigoid is suspected, Jentadueto should be discontinued.

Vitamin B12

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, appears to be rapidly reversible with discontinuation of metformin or Vitamin B12 supplementation. It is recommended that vitamin B12 serum levels are monitored annually. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency (see Section 4.8 Adverse effects (Undesirable effects).

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. TRAJENTA 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 TRAJENTA in paediatric patients under 18 years of age have not been established. A clinical trial did not demonstrate efficacy of linagliptin in paediatric patients 10 to 17 years of age. Linagliptin has not been studied in paediatric patients under 10 years of age.

Effects on laboratory tests

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. However, such studies have been conducted with the individual active substances, i.e. linagliptin and metformin. Co-administration of multiple doses of linagliptin and metformin did not meaningfully alter the pharmacokinetics of either linagliptin or metformin in healthy volunteers and patients.

Linagliptin

In vitro assessment of interactions

Linagliptin is a weak competitive and a weak to moderate mechanism-based inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes. It is not an inducer of CYP isozymes.

Linagliptin is a P-glycoprotein substrate, and inhibits P-glycoprotein mediated transport of digoxin with low potency. Based on these results and *in vivo* drug interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates.

In vivo assessment of interactions

Effects of other medicinal products on linagliptin

Clinical data described below suggest that the risk for clinically meaningful interactions by coadministered medicinal products is low.

Metformin:

Co-administration of multiple three-times-daily doses of 850 mg metformin hydrochloride with 10 mg linagliptin once daily did not clinical meaningfully alter the pharmacokinetics of linagliptin in healthy subjects.

Sulphonylureas:

The steady-state pharmacokinetics of 5 mg linagliptin were not changed by concomitant administration of a single 1.75 mg dose glibenclamide (glyburide).

Ritonavir:

Co-administration of a single 5 mg oral dose of linagliptin and multiple 200 mg oral doses of ritonavir, a potent inhibitor of P-glycoprotein and CYP3A4, increased the AUC and C_{max} of linagliptin approximately twofold and threefold, respectively. The unbound concentrations, which are usually less than 1% at the therapeutic dose of linagliptin, were increased 4-5-fold after co-administration with ritonavir. Simulations of steady-state plasma

concentrations of linagliptin with and without ritonavir indicated that the increase in exposure will not be associated with an increased accumulation. These changes in linagliptin pharmacokinetics were not considered to be clinically relevant. Therefore, clinically relevant interactions would not be expected with other P-glycoprotein/CYP3A4 inhibitors.

Rifampicin:
Multiple co-administration of 5 mg linagliptin with rifampicin, a potent inductor of P-glycoprotein and CYP3A4, resulted in a 39.6% and 43.8% decreased linagliptin steady-state AUC and Cmax respectively, and about 30% decreased DPP-4 inhibition at trough. Thus full efficacy of linagliptin in combination with strong P-gp inducers might not be achieved, particularly if these are administered long-term. Co-administration with other potent inducers of P-glycoprotein and CYP3A4, such as carbamazepine, phenobarbital and phenytoin has not been studied.

Effects of linagliptin on other medicinal products
In clinical studies, as described below, linagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glyburide, simvastatin, warfarin, digoxin or oral contraceptives providing *in vivo* evidence of a low propensity for causing interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-glycoprotein, and organic cationic transporter (OCT).

Metformin:
Co-administration of multiple daily doses of 10 mg linagliptin with 850 mg metformin hydrochloride, an OCT substrate, had no relevant effect on the pharmacokinetics of metformin in healthy subjects. Therefore, linagliptin is not an inhibitor of OCT-mediated transport.

Sulphonylureas:
Co-administration of multiple oral doses of 5 mg linagliptin and a single oral dose of 1.75 mg

glibenclamide (glyburide) resulted in clinically not relevant reduction of 14% of both AUC and Cmax of glibenclamide. Because glibenclamide is primarily metabolised by CYP2C9, these data also support the conclusion that linagliptin is not a CYP2C9 inhibitor. Clinically meaningful interactions would not be expected with other sulphonylureas (e.g., glipizide, tolbutamide, and glimepiride) which, like glibenclamide, are primarily eliminated by CYP2C9.

Digoxin:
Co-administration of multiple daily doses of 5 mg linagliptin with multiple doses of 0.25 mg digoxin had no effect on the pharmacokinetics of digoxin in healthy subjects. Therefore, linagliptin is not an inhibitor of P-glycoprotein-mediated transport *in vivo.*

Warfarin:
Multiple daily doses of 5 mg linagliptin did not alter the pharmacokinetics of S(-) or R(+) warfarin, a CYP2C9 substrate, administered in a single dose.

Simvastatin:
Multiple daily doses of linagliptin had a minimal effect on the steady-state pharmacokinetics of simvastatin, a sensitive CYP3A4 substrate, in healthy subjects. Following administration of a supratherapeutic dose of 10 mg linagliptin concomitantly with 40 mg of simvastatin daily for 6 days, the plasma AUC of simvastatin was increased by 34%, and the plasma C_{max} by 10%.

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

Metformin
Combination requiring precautions for use
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.

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.

Organic cation transporters (OCT)
Metformin is a substrate of both transporters OCT1 and OCT2. Co-administration of metformin with

- 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.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are coadministered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

Concomitant use not recommended Alcohol
Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

Iodinated contrast agents
Jentadueto must 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 and 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy
The use of linagliptin has not been studied in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
A limited amount of data suggests that the use of metformin in pregnant women is not associated with an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with respect to reproductive toxicity (see section 5.3).
Non-clinical reproduction studies did not indicate an additive teratogenic effect attributed to the co- administration of linagliptin and metformin.
Jentadueto should not be used during pregnancy. If the patient plans to become pregnant, or if pregnancy occurs, treatment with Jentadueto should be discontinued and switched to insulin treatment as soon as possible in order to lower the risk of foetal malformations associated with abnormal blood glucose levels.

Breast-feeding
Studies in animals have shown excretion of both metformin and linagliptin into milk in lactating rats. Metformin is excreted in human milk in small amounts. It is not known whether linagliptin is excreted into human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Jentadueto therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
The effect of Jentadueto on human fertility has not been studied. No adverse effects of linagliptin on fertility were observed in male or female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Jentadueto has no or negligible influence on the ability to drive and use machines. However, patients should be alerted to the risk of hypoglycaemia when Jentadueto is used in combination with other anti- diabetic medicinal products known to cause hypoglycaemia (e.g. sulphonylureas).

4.8 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 requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

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 ≥ 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 ≥ 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 ≥ 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 TRAJENTA 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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 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 TRAJENTA

(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 ≥ 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 ≥ 10%, Common ≥ 1% and < 10%, Uncommon ≥ 0.1% and < 1%, Rare ≥ 0.01% and < 0.1%, Very rare < 0.01%.

System Organ Class Adverse reaction	**Metformin hydrochloride monotherapy**
Gastrointestinal disorders[1]	
Abdominal pain	very common
Decreased appetite	very common
Diarrhoea	very common
Nausea	very common
Vomiting	very common
Hepatobiliary disorders[2]	
Hepatitis	very rare
Liver function test abnormalities	very rare
Metabolism and nutrition disorder	
Vitamin B12 decrease/deficiency[3]	common
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 ≥1% and <10%, Uncommon

≥0.1% and <1%, Rare ≥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
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.

'Reporting of suspected adverse reactions:
Healthcare professionals are requested to report any suspected adverse reactions to the National Regulatory Agents

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 (adjuste	0.6	-0.5	-0.9	-1.8	-1.8	-2.7

d mean)						
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 ≥ 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.

<u>Linagliptin as add-on to a combination of metformin and sulfonylurea therapy</u>

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 ≥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 glimepride

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).

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 sulfonylurea 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 -1.1mmol/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 sulfonylurea 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 m^2, 28% of the population had eGFR ≥30 to <45 mL/min/1.73 m^2 and 15% had eGFR <30 mL/min/1.73 m^2.

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**

	Number of Subjects (%)	Incidence Rate per 1000 PY*	Number of Subjects (%)	Incidence Rate per 1000 PY*	(95% CI)
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

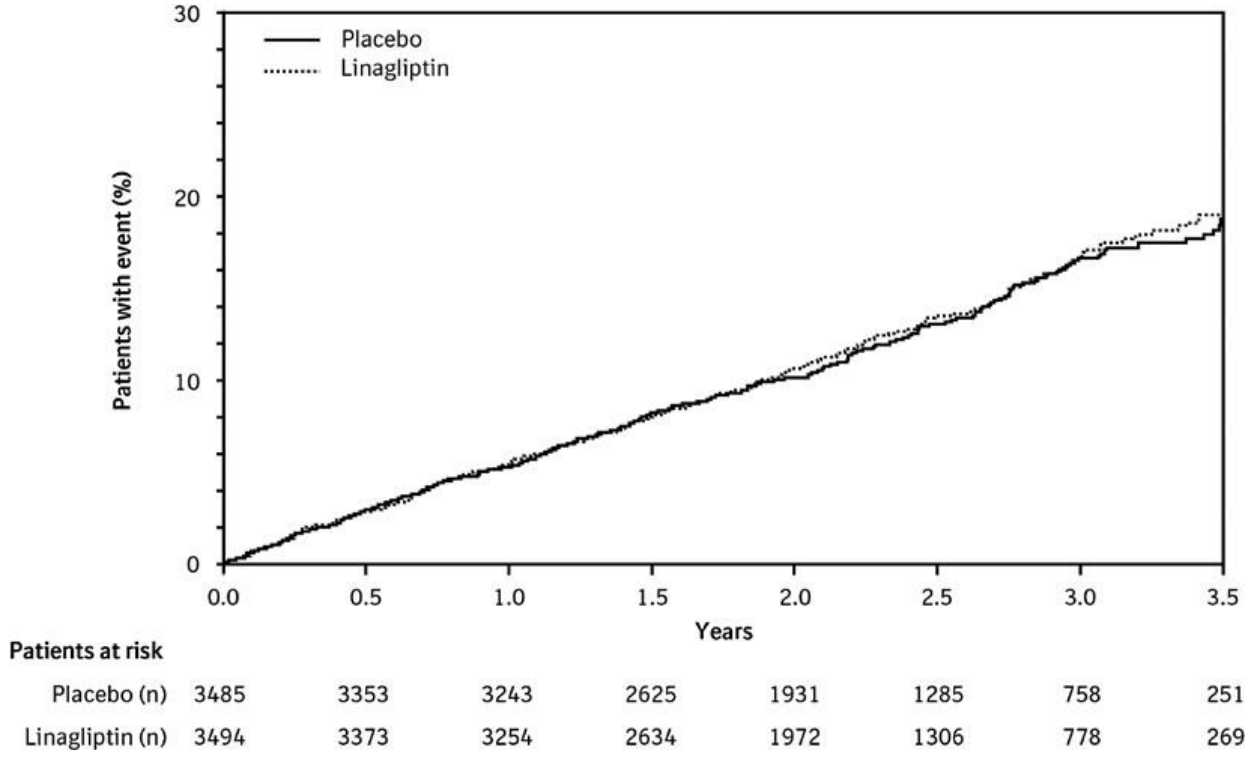


Table 8 Hospitalisation for heart failure and mortality by treatment group in the CARMELINA study

	Linagliptin 5mg	Placebo	Hazard Ratio

	Number of Subjects (%)	Incidence Rate per 1000 PY*	Number of Subjects (%)	Incidence Rate per 1000 PY*	(95% CI)
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 ≥ 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/1.73m^2 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**
	Number of Subjects (%)	Incidence Rate per 1000 PY*	Number of Subjects (%)	Incidence Rate per 1000 PY*	(95% CI)
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 TRAJENTA (linagliptin/metformin hydrochloride) combination tablets are bioequivalent to co-administration of linagliptin and metformin hydrochloride as individual tablets following a single dose.

Administration of TRAJENTA 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.

Excretion

Following administration of an oral [^{14}C]-linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated in faeces (80%) or urine (5%) within 4 days of dosing. Renal clearance at steady state was approximately 70 mL/min.

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

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.

TRAJENTA treatment should not be initiated in patients ≥ 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 - age (years)] x weight (kg) {x 0.85 for female patients} / [72 x 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 TRAJENTA contains the following inactive ingredients: arginine, maize starch, copovidone, colloidal anhydrous silica, magnesium stearate, titanium dioxide, propylene glycol, hypromellose, purified talc, iron oxide yellow (TRAJENTA 2.5 mg/500 mg; TRAJENTA 2.5 mg/850 mg) and/or iron oxide red (TRAJENTA 2.5 mg/850 mg; TRAJENTA 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

TRAJENTA 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: pKa1 = 8.6; pKa2 = 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 pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

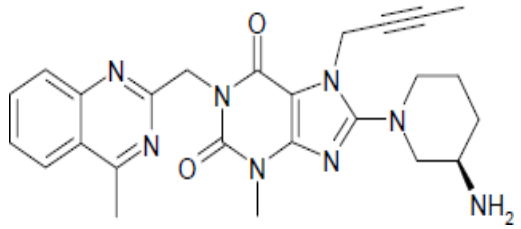
Chemical structure

Linagliptin

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

Molecular formula: $C_{25}H_{28}N_8O_2$ Molecular weight: 472.54

Structural formula:

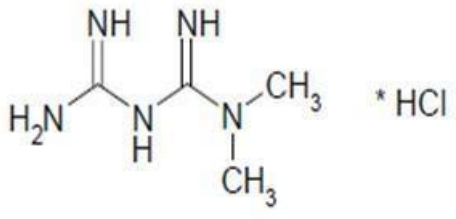


Metformin hydrochloride

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

Boehringer Ingelheim Pty Limited ABN 52 000 452 308

78 Waterloo Road
North Ryde NSW
2113
www.boehringer-ingelheim.com.au

9 DATE OF FIRST APPROVAL

21 May 2013

10 DATE OF REVISION

5. PHARMACEUTICAL PARTICULARS

5.1 List of excipients

Tablet core
Arginine
Copovidone
Magnesium
stearate Maize
starch
Silica, colloidal anhydrous

Jentadueto 2.5 mg/850 mg film-coated tablets
Film coating
Hypromellose
Titanium dioxide
(E171) Talc
Yellow iron oxide
(E172) Red iron oxide
(E172) Propylene
glycol

Jentadueto 2.5 mg/1,000 mg film-coated tablets
Film coating
Hypromellose
Titanium dioxide
(E171) Talc
Red iron oxide
(E172) Propylene
glycol

5.2 Incompatibilities

Not applicable.

5.3 Shelf life

18 months.

5.4 Special precautions for storage

This medicinal product does not require any special temperature

storage conditions. Blister
Store in the original package in order to protect from moisture.

Bottle
Keep the bottle tightly closed in order to protect from moisture.

5.5 Nature and contents of container

- Pack sizes of 60 film-coated tablets in aluminium lidding foil and PVC/polychlorotrifluoro ethylene/PVC based forming foil perforated unit dose blisters.

- High-Density PolyEthylene (HDPE) bottle with plastic screw cap and a seal liner (aluminium- polyester foil laminate) and a silica gel desiccant. Pack sizes of 60 film-coated tablets.

Not all pack sizes may be marketed.

5.6 Special precautions for disposal

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

6. MARKETING AUTHORISATION HOLDER

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

7. MARKETING AUTHORISATION NUMBER(S)

Jentadueto 2.5 mg/850 mg film-coated tablets EU/1/12/780/001 (10 x 1 film-coated tablets)
EU/1/12/780/002 (14 x 1 film-coated tablets)
EU/1/12/780/003 (28 x 1 film-coated tablets)
EU/1/12/780/004 (30 x 1 film-coated tablets)
EU/1/12/780/005 (56 x 1 film-coated tablets)
EU/1/12/780/006 (60 x 1 film-coated tablets)
EU/1/12/780/007 (84 x 1 film-coated tablets)
EU/1/12/780/008 (90 x 1 film-coated tablets)
EU/1/12/780/009 (98 x 1 film-coated tablets)
EU/1/12/780/010 (100 x 1 film-coated tablets)
EU/1/12/780/011 (120 x 1 film-coated tablets) EU/1/12/780/012 (14 film-coated tablets, bottle) EU/1/12/780/013 (60 film-coated tablets, bottle) EU/1/12/780/014 (180 film-coated tablets, bottle)
EU/1/12/780/029 (120 (2 x 60 x 1) film-

coated tablets)
EU/1/12/780/030 (180 (2 x 90 x 1) film-coated tablets)
EU/1/12/780/031 (200 (2 x 100 x 1) film-coated tablets)
EU/1/12/780/035 (180 (3 x 60 x 1) film-coated tablets)

Kenya: H2013/CTD1293/346 (60)

Jentadueto 2.5 mg/1,000 mg film-coated tablets EU/1/12/780/015 (10 x 1 film-coated tablets)
EU/1/12/780/016 (14 x 1 film-coated tablets)
EU/1/12/780/017 (28 x 1 film-coated tablets)
EU/1/12/780/018 (30 x 1 film-coated tablets)
EU/1/12/780/019 (56 x 1 film-coated tablets)
EU/1/12/780/020 (60 x 1 film-coated tablets)
EU/1/12/780/021 (84 x 1 film-coated tablets)
EU/1/12/780/022 (90 x 1 film-coated tablets)
EU/1/12/780/023 (98 x 1 film-coated tablets)
EU/1/12/780/024 (100 x 1 film-coated tablets)
EU/1/12/780/025 (120 x 1 film-coated tablets) EU/1/12/780/026 (14 film-coated tablets, bottle) EU/1/12/780/027 (60 film-coated tablets, bottle) EU/1/12/780/028 (180 film-coated tablets, bottle)
EU/1/12/780/032 (120 (2 x 60 x 1) film-coated tablets)
EU/1/12/780/033 (180 (2 x 90 x 1) film-coated tablets)
EU/1/12/780/034 (200 (2 x 100 x 1) film-coated tablets)
EU/1/12/780/036 (180 (3 x 60 x 1) film-coated tablets)

Kenya: H2013/CTD1295/344 (60)

8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 July 2012

Date of latest renewal: 22 March 2017

9. DATE OF REVISION OF THE TEXT