Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Linagliptin/Metformin hydrochloride 2.5 mg/1000 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5 mg of linagliptin and 1,000 mg of metformin hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Pink, oval-shaped, biconvex film-coated tablet with break-line on one side and debossed with '2.5/1000' on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Linagliptin/Metformin hydrochloride Rowex 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 linagliptin/metformin combination 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 linagliptin/metformin combination 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, linagliptin/metformin combination 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 linagliptin/metformin combination 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 linagliptin/metformin combination 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, [Nationally completed name] 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, linagliptin/metformin combination 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

A GFR 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.

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

If no adequate strength of [Nationally completed name] is available, individual monocomponents should be used instead of the fixed dose combination.

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

Linagliptin/Metformin hydrochloride Rowex is not recommended in patients with hepatic impairment due to the active substance metformin (see sections 4.3 and 5.2). Clinical experience with linagliptin/metformin combination in patients with hepatic impairment is lacking.

Paediatric population

A clinical trial did not establish efficacy in paediatric patients 10 to 17 years of age (see section 4.8, and 5.2). Therefore, treatment of children and adolescents with linagliptin is not recommended. Linagliptin has not been studied in paediatric patients under 10 years of age.

Method of administration

Linagliptin/Metformin hydrochloride Rowex 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
Linagliptin/Metformin hydrochloride Rowex 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 Linagliptin/Metformin hydrochloride Rowex 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 hypoglycaemia 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 dyspnoea, 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.

Patients with known or suspected mitochondrial diseases
In patients with known mitochondrial diseases such as Mitochondrial Encephalopathy with Lactic Acidosis, and Stroke-like episodes (MELAS) syndrome and Maternal inherited diabetes and deafness (MIDD), metformin is not recommended due to the risk of lactic acidosis exacerbation and neurologic complications which may lead to worsening of the disease.
In case of signs and symptoms suggestive of MELAS syndrome or MIDD after the intake of metformin, treatment with metformin should be withdrawn immediately and prompt diagnostic evaluation should be performed.

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, linagliptin/metformin combination may be used with a regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, linagliptin/metformin combination is contraindicated (see section 4.3).

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.

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 linagliptin/metformin combination contains metformin, a patient with previously well controlled type 2 diabetes on linagliptin/metformin combination 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, linagliptin/metformin combination 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, linagliptin/metformin combination should be discontinued; if acute pancreatitis is confirmed, linagliptin/metformin combination 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, linagliptin/metformin combination should be discontinued.

Vitamin B12
Metformin may reduce vitamin B12 levels. 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. In case of suspicion of vitamin B12 deficiency (such as anaemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

Linagliptin/Metformin hydrochloride Rowex contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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 C_{max} respectively, and about 30% decreased DPP-4 inhibition at trough. Thus full efficacy of linagliptin in combination with strong P-gp inducers might not be achieved, particularly if these are administered long-term. Co-administration with other potent inducers of P-glycoprotein and CYP3A4, such as carbamazepine, phenobarbital and phenytoin has not been studied.

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 C_{max} of glibenclamide. Because glibenclamide is primarily metabolised by CYP2C9, these data also support the conclusion that linagliptin is not a CYP2C9 inhibitor. Clinically meaningful interactions would not be expected with other sulphonylureas (e.g., glipizide, tolbutamide, and glimepiride) which, like glibenclamide, are primarily eliminated by CYP2C9.

Digoxin:
Co-administration of multiple daily doses of 5 mg linagliptin with multiple doses of 0.25 mg digoxin had no effect on the pharmacokinetics of digoxin in healthy 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
Linagliptin/metformin combination 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.
Linagliptin/metformin combination should not be used during pregnancy. If the patient plans to become pregnant, or if pregnancy occurs, treatment with linagliptin/metformin combination 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 linagliptin/metformin combination therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
The effect of linagliptin/metformin combination 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

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

4.8 Undesirable effects

Summary of the safety profile
The safety of linagliptin 2.5 mg twice daily (or its bioequivalent of 5 mg once daily) in combination with metformin has been evaluated in over 6800 patients with type 2 diabetes mellitus. In placebo-controlled studies, more than 1800 patients were treated with the therapeutic dose of either 2.5 mg linagliptin twice daily (or its bioequivalent of 5 mg linagliptin once daily) in combination with metformin for ≥ 12/24 weeks.

In the pooled analysis of the seven placebo-controlled trials, the overall incidence of adverse events in patients treated with placebo and metformin was comparable to that seen with linagliptin 2.5 mg and metformin (54.3 and 49.0%). Discontinuation of therapy due to adverse events was comparable in patients who received placebo and metformin to patients treated with linagliptin and metformin (3.8% and 2.9%).

The most frequently reported adverse reaction for linagliptin plus metformin was diarrhoea (1.6%) with a comparable rate on metformin plus placebo (2.4%).

Hypoglycaemia may occur when linagliptin/metformin combination is administered together with sulphonylurea (≥ 1 case per 10 patients).

Tabulated list of adverse reactions
Adverse reactions reported in all clinical trials with the linagliptin+metformin combination or the use of the monocomponents (linagliptin or metformin) in clinical trials or from post-marketing experience are shown below according to system organ class. Adverse reactions previously reported with one of the individual active substances may be potential adverse reactions with linagliptin/metformin combination, even if not observed in clinical trials 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 2: Adverse reactions reported in patients who received linagliptin+metformin alone (as mono-components or in combination) or as add-on to other anti-diabetic therapies in clinical trial and from post-marketing experience

System organ class Adverse reaction	**Frequency of adverse reaction**
Infections and infestations	
Nasopharyngitis	uncommon
Immune system disorders	
Hypersensitivity (e.g. bronchial hyperreactivity)	uncommon
Metabolism and nutrition disorders	
Hypoglycaemia [1]	very common
Lactic acidosis [§]	very rare
Vitamin B12 decrease/deficiency [§, †]	common

Nervous system disorders	
Taste disturbance [§]	common
Respiratory, thoracic and mediastinal disorders	
Cough	uncommon
Gastrointestinal disorders	
Decreased appetite	uncommon
Diarrhoea	common
Nausea	common
Pancreatitis	rare #
Vomiting	uncommon
Constipation [2]	uncommon
Abdominal pain [§]	very common
Hepatobiliary disorders	
Liver function disorders [2]	uncommon
Hepatitis [§]	very rare
Skin and subcutaneous tissue disorders	
Angioedema	rare
Urticaria	rare
Infections and infestations	
Nasopharyngitis	uncommon
Erythema [§]	very rare
Rash	uncommon
Pruritus	uncommon
Bullous pemphigoid	rare #
Investigations	
Amylase increased	uncommon
Lipase increased*	common

* Based on lipase elevations >3 × ULN observed in clinical trials

\# Based on *Linagliptin cardiovascular and renal safety study (CARMELINA)*, see also below

[§] Identified adverse reactions of metformin monotherapy. Refer to Summary of Product Characteristics for metformin for additional information

[†] See section 4.4

[1] Adverse reaction observed in combination of linagliptin/metformin combination with sulphonylurea

[2] Adverse reaction observed in combination of linagliptin/metformin combination with insulin

Description of selected adverse reactions

Hypoglycaemia

In one study linagliptin was given as add-on to metformin plus sulphonylurea. When linagliptin and metformin were administered in combination with a sulphonylurea, hypoglycaemia was the most frequently reported adverse event (linagliptin plus metformin plus sulphonylurea 23.9% and 16.0% in placebo plus metformin plus sulphonylurea).

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

Other adverse reactions

Gastrointestinal disorders such as, nausea, vomiting, diarrhoea and decreased appetite and abdominal pain occur most frequently during initiation of therapy with linagliptin/metformin combination or metformin hydrochloride and resolve spontaneously in most cases. For prevention, it is recommended that linagliptin/metformin combination be taken during or after meals. A slow increase in dose of metformin hydrochloride may also improve gastrointestinal tolerability.

Linagliptin cardiovascular 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). 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 HbA_{1c} and CV risk factors. 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
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
HPRA Pharmacovigilance; website: www.hpra.ie.

4.9 Overdose

Linagliptin
During controlled clinical trials in healthy subjects, single doses of up to 600 mg linagliptin (equivalent to 120 times the recommended dose) were not associated with a dose dependent increase in adverse events. There is no experience with doses above 600 mg in humans.

Metformin
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. The most effective method to remove lactate and metformin hydrochloride is haemodialysis.

Management
In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g. remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute clinical measures if required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD11

Linagliptin/metformin combination combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: linagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Linagliptin
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 binds very effectively to DPP-4 in a reversible manner and thus leads to a sustained increase and a prolongation of active incretin levels. Linagliptin glucose-dependently increases insulin secretion and lowers

glucagon secretion thus resulting in an overall improvement in the glucose homeostasis. Linagliptin binds selectively to DPP-4 and exhibits a > 10,000 fold selectivity *versus* DPP-8 or DPP-9 activity *in vitro*.

Metformin
Mechanism of action
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 efficacy and safety

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 HbA_{1c}, (-0.64% change compared to placebo), from a mean baseline HbA_{1c} of 8%. Linagliptin also showed significant improvements in fasting plasma glucose (FPG) by -21.1 mg/dl and 2-hour post- prandial glucose (PPG) by -67.1 mg/dl compared to placebo, as well as a greater portion of patients achieving a target HbA_{1c} of < 7.0% (28.3% on linagliptin *versus* 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 1,000 mg twice daily) provided significant improvements in glycaemic parameters compared with either monotherapy as summarised in Table 3 (mean baseline HbA_{1c} 8.65%).

Table 3: 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**[1]	**Metformin HCl 500 mg Twice Daily**	**Linagliptin 2.5 mg Twice Daily**[1] **+ Metformin HCl 500 mg Twice Daily**	**Metformin HCl 1,000 mg Twice Daily**	**Linagliptin 2.5mg Twice Daily**[1] **+Metformin HCl 1,000 mg Twice Daily**
HbA_{1c}(%)						
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 HbA_{1c} <7%	7 (10.8)	14 (10.4)	27 (19.1)	42 (30.7)	43 (31.2)	76 (54.3)
Patients (%) receiving rescue treatment	29.2	11.1	13.5	7.3	8.0	4.3
FPG(mg/dL)						
Number of patients	n = 61	n = 134	n = 136	n = 135	n = 132	n = 136
Baseline (mean)	203	195	191	199	191	196

Change from baseline (adjusted mean)	10	-9	-16	-33	-32	-49
Difference from placebo (adjusted mean) (95% CI)	--	-19 (-31, -6)	-26 (-38, -14)	-43 (-56, -31)	-42 (-55, -30)	-60 (-72, -47)

[1] Total daily dose of linagliptin is equal to 5 mg

Mean reductions from baseline in HbA_{1c} were generally greater for patients with higher baseline HbA_{1c} 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 in weight 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%).

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 5 mg once daily and 2.5 mg twice daily provided comparable (CI: -0.07; 0.19) significant HbA_{1c} 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. Body weight did not differ significantly between the groups.

Linagliptin as add-on to a combination of metformin and sulphonylurea therapy
A placebo-controlled study of 24 weeks in duration was conducted to evaluate the efficacy and safety of linagliptin 5 mg to placebo, in patients not sufficiently treated with a combination with metformin and a sulphonylurea. Linagliptin provided significant improvements in HbA_{1c} (-0.62% change compared to placebo), from a mean baseline HbA_{1c} of 8.14%. Linagliptin also showed significant improvements in patients achieving a target HbA_{1c} of < 7.0% (31.2% on linagliptin *versus* 9.2% on placebo), and also for fasting plasma glucose (FPG) with -12.7 mg/dl reduction compared to placebo. Body weight did not differ significantly between the groups.

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 HbA_{1c} in this subgroup with -0.68% (CI: -0.78; -0,57) adjusted mean change from baseline (mean baseline HbA_{1c} 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 24-month data, as add-on to metformin in comparison with glimepiride
In a study comparing the efficacy and safety of the addition of linagliptin 5 mg or glimepiride (mean dose 3 mg) in patients with inadequate glycaemic control on metformin monotherapy, mean reductions in HbA_{1c} were -0.16% with linagliptin (mean baseline HbA_{1c} 7.69%) and -0.36% with glimepiride (mean baseline HbA_{1c} 7.69%.) with a mean treatment difference of 0.20% (97.5% CI: 0.09, 0.299).
The incidence of hypoglycaemia in the linagliptin group (7.5%) was significantly lower than that in the glimepiride group (36.1%). Patients treated with linagliptin exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glimepiride (-1.39 *versus* +1.29 kg).

Linagliptin as add-on therapy in elderly (age ≥ 70 years) with type 2 diabetes
The efficacy and safety of linagliptin in elderly (age ≥ 70 years) with type 2 diabetes was evaluated in a double-blind study of 24 weeks duration. Patients received metformin and/or sulphonylurea and/or insulin as background therapy. Doses of background anti-diabetic therapy were kept stable during the first 12 weeks, after which adjustments were permitted. Linagliptin provided significant improvements in HbA_{1c} (-0.64% change compared to placebo after 24 weeks), from a mean baseline HbA_{1c} of 7.8%. Linagliptin also showed significant improvements in fasting plasma glucose (FPG) compared to placebo. Body weight did not differ significantly between the groups.

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 HbA_{1c} parameters with -0.81% (CI: -1.01; -0.61) adjusted mean change from baseline (mean baseline HbA_{1c} 8.13%) compared to placebo in combination with metformin plus insulin.

Linagliptin cardiovascular and renal safety study (CARMELINA)
CARMELINA was a randomized 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 HbA_{1c}, 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 HbA_{1c} 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.

After a median follow up of 2.2 years, linagliptin, when added to standard of care, did not increase the risk of major adverse cardiovascular events or renal outcome events. There was no increased risk in hospitalization for heart failure which was an additional adjudicated endpoint observed compared to standard of care without linagliptin in patients with type 2 diabetes (table 4).

Table 4: Cardiovascular and renal outcomes by treatment group in the CARMELINA study

	Linagliptin 5 mg		**Placebo**		**Hazard Ratio**
	Number of Subjects (%)	Incidence Rate per 1000 PY*	Number of Subjects (%)	Incidence Rate per 1000 PY*	(95% CI)
Number of patients	3494		3485		
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)
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)
Hospitalization for heart failure	209 (6.0)	27.7	226 (6.5)	30.4	0.90 (0.74, 1.08)

* 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

In analyses for albuminuria progression (change from normoalbuminuria to micro- or macroalbuminuria, or from microalbuminuria to macroalbuminuria) the estimated hazard ratio was
0.86 (95% CI 0.78, 0.95) for linagliptin *versus* placebo.

Linagliptin cardiovascular safety study (CAROLINA)
CAROLINA was a randomized study in 6,033 patients with early type 2 diabetes and increased CV risk or established complications who were treated with linagliptin 5 mg (3,023) or glimepiride 1-4mg (3,010) added to standard of care (including background therapy with metformin in 83% of patients) targeting regional standards for HbA_{1c} and CV risk factors. The mean age for study population was 64 years and included 2,030 (34%) patients ≥ 70 years of age. The study population included 2,089 (35%) patients with cardiovascular disease and 1,130 (19%) patients with renal impairment with an eGFR < 60 mL/min/1.73m^2 at baseline. The mean HbA_{1c} 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 5) as compared to glimepiride. Results were consistent for patients treated with or without metformin.

Table 5: Major adverse cardiovascular events (MACE) and mortality by treatment group in the CAROLINA study

	Linagliptin		**Glimepiride**		**Hazard Ratio**

	5 mg		**(1-4 mg)**		
	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)**
All-cause mortality	308 (10.2)	16.8	336 (11.2)	18.4	0.91 (0.78,1.06)
CV death	169 (5.6)	9.2	168 (5.6)	9.2	1.00 (0.81, 1.24)
Hospitalization for heart failure (HHF)	112 (3.7)	6.4	92 (3.1)	5.3	1.21 (0.92, 1.59)

* 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.

Metformin

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1,000 patient-years) *versus* diet alone (43.3 events/1,000 patient-years), p=0.0023, and *versus* the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p=0.0034,

- a significant reduction of the absolute risk of any diabetes-related mortality: metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p=0.017,
- a significant reduction of the absolute risk of overall mortality: metformin13.5 events/1,000 patient-years *versus* diet alone 20.6 events/1,000 patient-years, (p=0.011), and *versus* the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient- years (p=0.021),
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years, (p=0.01).

5.2 Pharmacokinetic properties

Bioequivalence studies in healthy subjects demonstrated that the linagliptin/metformin hydrochloride combination tablets are bioequivalent to co-administration of linagliptin and metformin hydrochloride as individual tablets.

Administration of linagliptin/metformin combination 2.5/1,000 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 meaningful.

The following statements reflect the pharmacokinetic properties of the individual active substances of linagliptin/metformin combination.

Linagliptin

The pharmacokinetics of linagliptin has been extensively characterised in healthy subjects and patients with type 2 diabetes. After oral administration of a 5 mg dose to healthy volunteers or patients, linagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1.5 hours post-dose.

Plasma concentrations of linagliptin decline in a triphasic manner with a long terminal half-life (terminal half-life for linagliptin more than 100 hours), that is mostly related to the saturable, tight binding of linagliptin to DPP-4 and does not contribute to the accumulation of the active substance. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of 5 mg linagliptin, is approximately 12 hours. After once daily dosing of 5 mg linagliptin, steady-state plasma concentrations are reached by the third dose. Plasma AUC of linagliptin increased approximately 33% following 5 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for linagliptin AUC were small (12.6% and 28.5%, respectively). Due to the concentration dependent binding of linagliptin to DPP-

IV, the pharmacokinetics of linagliptin based on total exposure is not linear; indeed total plasma AUC of linagliptin increased in a less than dose-proportional manner, while unbound AUC increases in a roughly dose-proportional manner. The pharmacokinetics of linagliptin was generally similar in healthy subjects and in patients with type 2 diabetes.

Absorption
The absolute bioavailability of linagliptin is approximately 30%. Co-administration of a high-fat meal with linagliptin prolonged the time to reach C_{max} by 2 hours and lowered C_{max} by 15%, but no influence on AUC_{0-72h} was observed. No clinically relevant effect of C_{max} and T_{max} changes is expected; therefore linagliptin may be administered with or without food.

Distribution
As a result of tissue binding, the mean apparent volume of distribution at steady-state following a single 5 mg intravenous dose of linagliptin to healthy subjects is approximately 1,110 litres, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent, decreasing from about 99% at 1 nmol/L to 75-89% at ≥ 30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin At high concentrations, where DPP-4 is fully saturated, 70-80% of linagliptin was bound to other plasma proteins than DPP-4, hence 20-30% were unbound in plasma.

Biotransformation
Following a [^{14}C] linagliptin oral 10 mg dose, approximately 5% of the radioactivity was excreted in urine. Metabolism plays a subordinate role in the elimination of linagliptin. One main metabolite with a relative exposure of 13.3% of linagliptin at steady-state was detected which was found to be pharmacologically inactive, and thus does not contribute to the plasma DPP-4 inhibitory activity of linagliptin.

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

Renal impairment
Under steady-state conditions, linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects. In moderate renal impairment, a moderate increase in exposure of about 1.7 fold was observed compared with control. Exposure in T2DM patients with severe RI was increased by about 1.4 fold compared to T2DM patients with normal renal function. Steady-state predictions for AUC of linagliptin in patients with ESRD indicated comparable exposure to that of patients with moderate or severe renal impairment. In addition, linagliptin is not expected to be eliminated to a therapeutically significant degree by haemodialysis or peritoneal dialysis. No dose adjustment of linagliptin is recommended in patients with renal impairment; therefore, linagliptin may be continued as a single entity tablet at the same total daily dose of 5 mg if linagliptin/metformin combination is discontinued due to evidence of renal impairment.

Hepatic impairment
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.

Body Mass Index (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. The clinical trials before marketing authorization have been performed up to a BMI equal to 40 kg/m^2.

Gender
Gender had no clinically relevant effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data.

Elderly
Age did not have a clinically relevant impact on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. Older subjects (65 to 80 years, oldest patient was 78 years) had comparable plasma concentrations of linagliptin compared to younger subjects. Linagliptin trough concentrations were also measured in elderly (age ≥ 70 years) with type 2 diabetes in a phase III study of 24 weeks duration. Linagliptin concentrations in this study were within the range of values previously observed in younger type 2 diabetes patients.

Paediatric population

A paediatric Phase 2 study examined the pharmacokinetics and pharmacodynamics of 1 mg and 5 mg linagliptin in children and adolescents ≥ 10 to < 18 years of age with type 2 diabetes mellitus. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects. Linagliptin 5 mg showed superiority over 1 mg with regard to trough DPP-4 inhibition (72% vs 32%, p=0.0050) and a numerically larger reduction with regard to adjusted mean change from baseline in HbA_{1c} (-0.63% vs -0.48%, n.s.). Due to the limited nature of the data set the results should be interpreted cautiously.

A paediatric Phase 3 study examined pharmacokinetics and pharmacodynamics (HbA1c change from baseline) of 5 mg linagliptin in children and adolescents 10 to 17 years of age with type 2 diabetes mellitus. The observed exposure-response relationship was generally comparable between paediatric and adult patients, however, with a smaller drug effect estimated in children. Oral administration of linagliptin resulted in exposure within the range observed in adult patients. The observed geometric mean trough concentrations and geometric mean concentrations at 1.5 hours post-administration (representing a concentration around tmax) at steady state were 4.30 nmol/L and 12.6 nmol/L, respectively. Corresponding plasma concentrations in adult patients were 6.04 nmol/L and 15.1 nmol/L.

Race
Race had no obvious effect on the plasma concentrations of linagliptin based on a composite analysis of available pharmacokinetic data, including patients of Caucasian, Hispanic, African, and Asian origin. In addition the pharmacokinetic characteristics of linagliptin were found to be similar in dedicated phase I studies in Japanese, Chinese and Caucasian healthy subjects and African American type 2 diabetes patients.

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

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

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

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

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

Biotransformation
Metformin hydrochloride is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination
Renal clearance of metformin hydrochloride is > 400 mL/min, indicating that metformin hydrochloride is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.
When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin hydrochloride in plasma.

Paediatric population
Single dose study: after single doses of metformin hydrochloride 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.

5.3 Preclinical safety data

Linagliptin plus metformin
General toxicity studies in rats for up to 13 weeks were performed with the co-administration of linagliptin and metformin. The only observed interaction between linagliptin and metformin was a reduction of body weight gain. No other additive toxicity caused by the combination of linagliptin and metformin was observed at AUC exposure levels up to 2 and 23 times human exposure, respectively.

An embryofoetal development study in pregnant rats did not indicate a teratogenic effect attributed to the co-administration of linagliptin and metformin at AUC exposure levels up to 4 and 30 times human exposure, respectively.

Linagliptin
Liver, kidneys and gastrointestinal tract are the principal target organs of toxicity in mice and rats at repeat doses of linagliptin of more than 300 times the human exposure.
In rats, effects on reproductive organs, thyroid and the lymphoid organs were seen at more than
1,500 times human exposure. Strong pseudo-allergic reactions were observed in dogs at medium doses, secondarily causing cardiovascular changes, which were considered dog-specific. Liver, kidneys, stomach, reproductive organs, thymus, spleen, and lymph nodes were target organs of toxicity in Cynomolgus monkeys at more than 450 times human exposure. At more than 100 times human exposure, irritation of the stomach was the major finding in these monkeys.

Linagliptin and its main metabolite did not show a genotoxic potential.
Oral 2-year carcinogenicity studies in rats and mice revealed no evidence of carcinogenicity in rats or male mice. A significantly higher incidence of malignant lymphomas only in female mice at the highest dose (> 200 times human exposure) is not considered relevant for humans (explanation: non- treatment related but due to highly variable background incidence). Based on these studies there is no concern for carcinogenicity in humans.

The NOAEL for fertility, early embryonic development and teratogenicity in rats was set at > 900 times the human exposure. The NOAEL for maternal-, embryo-fetal-, and offspring toxicity in rats was 49 times human exposure. No teratogenic effects were observed in rabbits at > 1,000 times human exposure. A NOAEL of 78 times human exposure was derived for embryo-fetal toxicity in rabbits, and for maternal toxicity the NOAEL was 2.1 times human exposure. Therefore, it is considered unlikely that linagliptin affects reproduction at therapeutic exposures in humans.

Metformin
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Copovidone
Maize starch
Sodium carbonate anhydrous (E500)
Crospovidone Type A (E1202)
Magnesium stearate (E470b)
Silica, colloidal anhydrous (E551)

Film coating
Hypromellose 2910, 5mPas (E464)
Titanium dioxide (E171)
Talc (E553b)
Propylene Glycol (E1520)
Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Packs containing 10, 30, 56, 60 and 90 film-coated tablets and multipacks containing 180 (2 packs of 90) and 180 (3 packs of 60) film-coated tablets in Aluminium-OPA/Alu/PVC blisters.

Packs containing 10 x 1, 30 x 1, 56 x 1, 60 x 1 and 90 x 1 film-coated tablets and multipacks containing 180 x 1 (2 packs of 90 x 1) and 180 x 1 (3 packs of 60 x 1) film-coated tablets in Aluminium-OPA/Alu/PVC perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/335/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd November 2024

10 DATE OF REVISION OF THE TEXT

September 2025