ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Jentadueto 2.5 mg/850 mg film-coated tablets
Jentadueto 2.5 mg/1 000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Jentadueto 2.5 mg/850 mg film-coated tablets
Each tablet contains 2.5 mg of linagliptin and 850 mg of metformin hydrochloride.

Jentadueto 2.5 mg/1 000 mg film-coated tablets
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).

Jentadueto 2.5 mg/850 mg film-coated tablets
Oval, biconvex, light orange, film-coated tablet of 19.2 mm × 9.4 mm debossed with "D2/850" on one side and the company logo on the other.

Jentadueto 2.5 mg/1 000 mg film-coated tablets
Oval, biconvex, light pink, film-coated tablet of 21.1 mm × 9.7 mm debossed with "D2/1000" on one side and the company logo on the other.

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
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 Jentadueto 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 3 000 mg. Dose reduction may be considered in relation to declining renal function.	No dose adjustment
45-59	Maximum daily dose is 2 000 mg The starting dose is at most half of the maximum dose.	No dose adjustment
30-44	Maximum daily dose is 1 000 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.

Paediatric population
A clinical trial did not establish efficacy in paediatric patients 10 to 17 years of age (see section 4.8,

5.1 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
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.

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, 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
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.

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
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

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 6 800 patients with type 2 diabetes mellitus. In placebo-controlled studies, more than 1 800 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 Jentadueto 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 Jentadueto, 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

System organ class Adverse reaction	Frequency of adverse reaction
Infections and infestations	
Nasopharyngitis	uncommon
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
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 Jentadueto with sulphonylurea

[2] Adverse reaction observed in combination of Jentadueto 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 Jentadueto or metformin hydrochloride and resolve spontaneously in most cases. For prevention, it is recommended that Jentadueto 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.

Paediatric population
Overall, in clinical trials in paediatric patients with type 2 diabetes mellitus aged 10 to 17 years, the safety profile of linagliptin was similar to that observed in the adult population.

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

4.9 Overdose

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

Jentadueto 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 2.5 mg 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 as add on to a combination of metformin and empagliflozin therapy
In patients inadequately controlled with metformin and empagliflozin (10 mg (n= 247) or 25 mg (n = 217)), 24-weeks treatment with add-on therapy of linagliptin 5 mg provided adjusted mean HbA_{1c} reductions from baseline by -0.53% (significant difference to add-on placebo -0.32% (95% CI -0.52, -0.13) and -0.58% (significant difference to add-on placebo -0.47% (95% CI -0.66; -0.28), respectively. A statistically significant greater proportion of patients with a baseline $HbA_{1c} \geq 7.0\%$ and treated with linagliptin 5 mg achieved a target HbA_{1c} of < 7% compared to placebo.

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 1 000 PY*	Number of Subjects (%)	Incidence Rate per 1 000 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)
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 1-4 mg (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/1.73 m^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 5 mg		**Glimepiride (1-4 mg)**		**Hazard Ratio**
	Number of Subjects (%)	Incidence Rate per 1 000 PY*	Number of Subjects (%)	Incidence Rate per 1 000 PY*	(95% CI)
Number of patients	3 023		3 010		
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: metformin 13.5 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).

Paediatric population

The clinical efficacy and safety of empagliflozin 10 mg with potential dose-increase to 25 mg or linagliptin 5 mg once daily has been studied in children and adolescents from 10 to 17 years of age with T2DM in a double-blind, randomised, placebo-controlled, parallel group study (DINAMO) over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks. 91% of patients in the study were on background therapy with metformin as adjunct to diet and exercise. At baseline, the mean HbA1c was 8.03%. Treatment with linagliptin 5 mg did not provide significant improvement in HbA1c. The treatment difference of adjusted mean change in HbA1c after 26 weeks between linagliptin and placebo was -0.34% (95% CI -0.99, 0.30; p=0.2935). The adjusted mean change in HbA1c from baseline was 0.33% in patients treated with linagliptin and 0.68% in patients treated with placebo (see section 4.2).

5.2 Pharmacokinetic properties

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

Administration of Jentadueto 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 Jentadueto.

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 $\geq$ 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 hemodialysis 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 Jentadueto 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 embryofetal 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
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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 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.

6.5 Nature and contents of container

- Pack sizes of 10 × 1, 14 × 1, 28 × 1, 30 × 1, 56 × 1, 60 × 1, 84 × 1, 90 × 1, 98 × 1, 100 × 1 and 120 × 1 film-coated tablets and multipacks containing 120 (2 packs of 60 × 1), 180 (2 packs of 90 × 1), 180 (3 packs of 60 × 1) and 200 (2 packs of 100 × 1) 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 14, 60 and 180 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

Jentadueto 2.5 mg/850 mg film-coated tablets
EU/1/12/780/001 (10 × 1 film-coated tablets)
EU/1/12/780/002 (14 × 1 film-coated tablets)
EU/1/12/780/003 (28 × 1 film-coated tablets)
EU/1/12/780/004 (30 × 1 film-coated tablets)
EU/1/12/780/005 (56 × 1 film-coated tablets)
EU/1/12/780/006 (60 × 1 film-coated tablets)
EU/1/12/780/007 (84 × 1 film-coated tablets)
EU/1/12/780/008 (90 × 1 film-coated tablets)
EU/1/12/780/009 (98 × 1 film-coated tablets)
EU/1/12/780/010 (100 × 1 film-coated tablets)
EU/1/12/780/011 (120 × 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 × 60 × 1) film-coated tablets)
EU/1/12/780/030 (180 (2 × 90 × 1) film-coated tablets)
EU/1/12/780/031 (200 (2 × 100 × 1) film-coated tablets)
EU/1/12/780/035 (180 (3 × 60 × 1) film-coated tablets)

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 July 2012
Date of latest renewal: 22 March 2017

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

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

Boehringer Ingelheim Hellas Single Member S.A.
5th km Paiania – Markopoulo
Koropi Attiki, 19441
Greece

Dragenopharm Apotheker Püschl GmbH
Göllstraße 1
84529 Tittmoning
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSUR)**

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

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

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Jentadueto 2.5 mg/850 mg film-coated tablets
linagliptin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2.5 mg of linagliptin and 850 mg of metformin hydrochloride

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

10 × 1 film-coated tablets
14 × 1 film-coated tablets
28 × 1 film-coated tablets
30 × 1 film-coated tablets
56 × 1 film-coated tablets
60 × 1 film-coated tablets
84 × 1 film-coated tablets
90 × 1 film-coated tablets
98 × 1 film-coated tablets
100 × 1 film-coated tablets
120 × 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/780/001 10 × 1 film-coated tablets
EU/1/12/780/002 14 × 1 film-coated tablets
EU/1/12/780/003 28 × 1 film-coated tablets
EU/1/12/780/004 30 × 1 film-coated tablets
EU/1/12/780/005 56 × 1 film-coated tablets
EU/1/12/780/006 60 × 1 film-coated tablets
EU/1/12/780/007 84 × 1 film-coated tablets
EU/1/12/780/008 90 × 1 film-coated tablets
EU/1/12/780/009 98 × 1 film-coated tablets
EU/1/12/780/010 100 × 1 film-coated tablets
EU/1/12/780/011 120 × 1 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jentadueto 2.5 mg/850 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Jentadueto 2.5 mg/850 mg tablets
linagliptin/metformin HCl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS – INTERMEDIATE CARTON WITHOUT BLUE BOX – 2.5 mg/850 mg FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Jentadueto 2.5 mg/850 mg film-coated tablets
linagliptin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2.5 mg of linagliptin and 850 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 × 1 film-coated tablets. Component of a multipack, cannot be sold separately.
90 × 1 film-coated tablets. Component of a multipack, cannot be sold separately.
100 × 1 film-coated tablets. Component of a multipack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/780/029 (120 (2 × 60 × 1) film-coated tablets)
EU/1/12/780/030 (180 (2 × 90 × 1) film-coated tablets)
EU/1/12/780/031 (200 (2 × 100 × 1) film-coated tablets)
EU/1/12/780/035 (180 (3 × 60 × 1) film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jentadueto 2.5 mg/850 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACKS – WRAPPED IN TRANSPARENT FOIL – INCLUDING THE BLUE BOX – 2.5 mg/850 mg FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Jentadueto 2.5 mg/850 mg film-coated tablets
linagliptin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2.5 mg of linagliptin and 850 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack comprising 2 packs, each containing 60 × 1 film-coated tablets
Multipack comprising 2 packs, each containing 90 × 1 film-coated tablets
Multipack comprising 2 packs, each containing 100 × 1 film-coated tablets
Multipack comprising 3 packs, each containing 60 × 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/780/029 (120 (2 × 60 × 1) film-coated tablets)
EU/1/12/780/030 (180 (2 × 90 × 1) film-coated tablets)
EU/1/12/780/031 (200 (2 × 100 × 1) film-coated tablets)
EU/1/12/780/035 (180 (3 × 60 × 1) film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jentadueto 2.5 mg/850 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Jentadueto 2.5 mg/1 000 mg film-coated tablets
linagliptin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

10 × 1 film-coated tablets
14 × 1 film-coated tablets
28 × 1 film-coated tablets
30 × 1 film-coated tablets
56 × 1 film-coated tablets
60 × 1 film-coated tablets
84 × 1 film-coated tablets
90 × 1 film-coated tablets
98 × 1 film-coated tablets
100 × 1 film-coated tablets
120 × 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/780/015 10 × 1 film-coated tablets
EU/1/12/780/016 14 × 1 film-coated tablets
EU/1/12/780/017 28 × 1 film-coated tablets
EU/1/12/780/018 30 × 1 film-coated tablets
EU/1/12/780/019 56 × 1 film-coated tablets
EU/1/12/780/020 60 × 1 film-coated tablets
EU/1/12/780/021 84 × 1 film-coated tablets
EU/1/12/780/022 90 × 1 film-coated tablets
EU/1/12/780/023 98 × 1 film-coated tablets
EU/1/12/780/024 100 × 1 film-coated tablets
EU/1/12/780/025 120 × 1 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jentadueto 2.5 mg/1 000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Jentadueto 2.5 mg/1 000 mg tablets
linagliptin/metformin HCl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS – INTERMEDIATE CARTON WITHOUT BLUE BOX – 2.5 mg/1 000 mg FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Jentadueto 2.5 mg/1 000 mg film-coated tablets
linagliptin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 × 1 film-coated tablets. Component of a multipack, cannot be sold separately.
90 × 1 film-coated tablets. Component of a multipack, cannot be sold separately.
100 × 1 film-coated tablets. Component of a multipack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/780/032 (120 (2 × 60 × 1) film-coated tablets)
EU/1/12/780/033 (180 (2 × 90 × 1) film-coated tablets)
EU/1/12/780/034 (200 (2 × 100 × 1) film-coated tablets)
EU/1/12/780/036 (180 (3 × 60 × 1) film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jentadueto 2.5 mg/1 000 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACKS – WRAPPED IN TRANSPARENT FOIL – INCLUDING THE BLUE BOX – 2.5 mg/1 000 mg FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Jentadueto 2.5 mg/1 000 mg film-coated tablets
linagliptin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack comprising 2 packs, each containing 60 × 1 film-coated tablets
Multipack comprising 2 packs, each containing 90 × 1 film-coated tablets
Multipack comprising 2 packs, each containing 100 × 1 film-coated tablets
Multipack comprising 3 packs, each containing 60 × 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/780/032 (120 (2 × 60 × 1) film-coated tablets)
EU/1/12/780/033 (180 (2 × 90 × 1) film-coated tablets)
EU/1/12/780/034 (200 (2 × 100 × 1) film-coated tablets)
EU/1/12/780/036 (180 (3 × 60 × 1) film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jentadueto 2.5 mg/1 000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND LABEL – HDPE BOTTLE (17 AND 18 APPLICABLE ONLY FOR CARTON)

1. NAME OF THE MEDICINAL PRODUCT

Jentadueto 2.5 mg/850 mg film-coated tablets
linagliptin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2.5 mg of linagliptin and 850 mg of metformin hydrochloride

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
60 film-coated tablets
180 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/780/012 14 film-coated tablets
EU/1/12/780/013 60 film-coated tablets
EU/1/12/780/014 180 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jentadueto 2.5 mg/850 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND LABEL – HDPE BOTTLE (17 AND 18 APPLICABLE ONLY FOR CARTON)

1. NAME OF THE MEDICINAL PRODUCT

Jentadueto 2.5 mg/1 000 mg film-coated tablets
linagliptin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
60 film-coated tablets
180 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/780/026 14 film-coated tablets
EU/1/12/780/027 60 film-coated tablets
EU/1/12/780/028 180 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jentadueto
2.5 mg/1 000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Jentadueto 2.5 mg / 850 mg film-coated tablets
Jentadueto 2.5 mg / 1 000 mg film-coated tablets
linagliptin/metformin hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Jentadueto is and what it is used for

The name of your tablet is Jentadueto. It contains two different active substances linagliptin and metformin.
- Linagliptin belongs to a class of medicines called DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors).
- Metformin belongs to a class of medicines called biguanides.

How Jentadueto works
The two active substances work together to control blood sugar levels in adult patients with a form of diabetes called ‘type 2 diabetes mellitus’. Along with diet and exercise, this medicine helps to improve the levels and effects of insulin after a meal and lowers the amount of sugar made by your body.

This medicine can be used alone or with certain other medicines for diabetes like sulphonylureas, empagliflozin, or insulin.

What is type 2 diabetes?

Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems like heart disease, kidney disease, blindness, and amputation.

2. What you need to know before you take Jentadueto

Do not take Jentadueto
- if you are allergic to linagliptin or metformin or any of the other ingredients of this medicine (listed in section 6).
- if you have severely reduced kidney function.
- if you have uncontrolled diabetes, with, for example, severe hyperglycaemia (high blood

glucose), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis (see "Risk of lactic acidosis" below) or ketoacidosis. Ketoacidosis is a condition in which substances called 'ketone bodies' accumulate in the blood and which can lead to diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or your breath developing an unusual fruity smell.
- if you ever had a diabetic pre-coma.
- if you have a severe infection such as an infection affecting your lung or bronchial system or your kidney. Severe infections may lead to kidney problems, which can put you at risk for lactic acidosis (see 'Warnings and precautions').
- if you have lost a lot of water from your body (dehydration), e.g. due to long-lasting or severe diarrhoea, or if you have vomited several times in a row. Dehydration may lead to kidney problems, which can put you at risk for lactic acidosis (see 'Warnings and precautions').
- if you are treated for acute heart failure or have recently had a heart attack, have severe problems with your circulation (such as shock) or have breathing difficulties. This may lead to a lack in oxygen supply to tissue which can put you at risk for lactic acidosis (see 'Warnings and precautions').
- if you have liver problems.
- if you drink alcohol to excess, either every day or only from time to time (see section 'Jentadueto with alcohol').

Do not take Jentadueto if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking this medicine.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Jentadueto
- if you have type 1 diabetes (your body does not produce any insulin). Jentadueto should not be used to treat this condition.
- if you are taking insulin or an anti-diabetic medicine known as 'sulphonylurea', your doctor may want to reduce your dose of insulin or sulphonylurea when you take either of them together with Jentadueto in order to avoid low blood sugar (hypoglycaemia).
- if you have or have had a disease of the pancreas.

If you have symptoms of acute pancreatitis, like persistent, severe abdominal pain, you should consult your doctor.

If you encounter blistering of the skin it may be a sign for a condition called bullous pemphigoid. Your doctor may ask you to stop Jentadueto.

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before taking Jentadueto.

Diabetic skin problems are a common complication of diabetes. You are advised to follow the recommendations for skin and foot care that you are given by your doctor or nurse.

Risk of lactic acidosis.
Due to the metformin component, Jentadueto may cause a very rare, but very serious complication called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration (see further information below), liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease).
If any of the above apply to you, talk to your doctor for further instructions.

Stop taking Jentadueto for a short time if you have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instruction.

Stop taking Jentadueto and contact a doctor or the nearest hospital immediately if you experience some of the symptoms of lactic acidosis, as this condition may lead to coma.
Symptoms of lactic acidosis include:
- vomiting
- stomach ache (abdominal pain)
- muscle cramps
- a general feeling of not being well with severe tiredness
- difficulty in breathing
- reduced body temperature and heartbeat

Talk to your doctor promptly for further instructions
- if you are known to suffer from a genetically inherited disease affecting mitochondria (the energy-producing components within cells) such as MELAS syndrome (Mitochondrial Encephalopathy, myopathy, Lactic acidosis and Stroke-like episodes) or Maternal inherited diabetes and deafness (MIDD).
- if you have any of these symptoms after starting metformin: seizure, declined cognitive abilities, difficulty with body movements, symptoms indicating nerve damage (e.g. pain or numbness), migraine and deafness.

Lactic acidosis is a medical emergency and must be treated in a hospital.

If you need to have major surgery you must stop taking Jentadueto during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with Jentadueto.

During treatment with Jentadueto, your doctor will check your kidney function at least once a year or more frequently if you are elderly and/or if you have worsening kidney function.

Children and adolescents
This medicine is not recommended for use in children and adolescents under 18 years. It is not effective in children and adolescents between the ages of 10 and 17 years. It is not known if this medicine is safe and effective when used in children younger than 10 years.

Other medicines and Jentadueto
If you need to have an injection of a contrast medium that contains iodine into your bloodstream, for example in the context of an X-ray or scan, you must stop taking Jentadueto before or at the time of the injection. Your doctor will decide when you must stop and when to restart your treatment with Jentadueto.

Tell your doctor if you are taking, have recently taken or might take any other medicines. You may need more frequent blood glucose and kidney function tests, or your doctor may need to adjust the dosage of Jentadueto. It is especially important to mention the following:
- medicines which increase urine production (diuretics)
- medicines used to treat pain and inflammation (NSAID and COX-2-inhibitors, such as ibuprofen and celecoxib)
- certain medicines for the treatment of high blood pressure (ACE inhibitors and angiotensin II receptor antagonists)
- medicines that may change the amount of metformin in your blood, especially if you have reduced kidney function (such as verapamil, rifampicin, cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole, crizotinib, olaparib).
- carbamazepine, phenobarbital or phenytoin. These may be used to control fits (seizures) or chronic pain.
- rifampicin. This is an antibiotic used to treat infections such as tuberculosis.
- medicines used to treat diseases that involve inflammation, like asthma and arthritis (corticosteroids).
- bronchodilators (β-sympathomimetics) for the treatment of bronchial asthma.
- alcohol-containing medicines.

Jentadueto with alcohol
Avoid excessive alcohol intake while taking Jentadueto since this may increase the risk of lactic acidosis (see section 'Warnings and precautions').

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

You should not use Jentadueto if you are pregnant. It is unknown if this medicine is harmful to the unborn child.

Metformin passes into human milk in small amounts. It is not known whether linagliptin passes into human milk. Talk to your doctor if you want to breast-feed while taking this medicine.

Driving and using machines
Jentadueto has no or negligible influence on the ability to drive and use machines.

However, taking Jentadueto in combination with medicines called sulphonylureas or with insulin can cause too low blood sugar level (hypoglycaemia), which may affect your ability to drive and use machines or work without safe foothold.

3. How to take Jentadueto

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
The amount of Jentadueto that you will take varies depending on your condition and the doses you currently take of metformin and/or individual tablets of linagliptin and metformin. Your doctor will tell you exactly the dose of this medicine to take.

How to take this medicine
- one tablet twice daily by mouth in the dose prescribed by your doctor.
- with meals to lower your chance of an upset stomach.

You should not exceed the maximum recommended daily dose of 5 mg linagliptin and 2 000 mg metformin hydrochloride.

Continue to take Jentadueto as long as your doctor prescribes it so you can continue to help control your blood sugar. Your doctor may prescribe this medicine together with another oral anti-diabetic medicine or insulin. Remember to take all medicines as directed by your doctor to achieve the best results for your health.

You should continue your diet during treatment with Jentadueto and take care that your carbohydrate intake is equally distributed over the day. If you are overweight, continue your energy-restricted diet as instructed. This medicine alone is unlikely to cause abnormally low blood sugar (hypoglycaemia). When Jentadueto is used with a sulphonylurea medicine or with insulin, low blood sugar can occur and your doctor may reduce the dose of your sulphonylurea or insulin.

If you take more Jentadueto than you should
If you take more Jentadueto tablets than you should have, you may experience lactic acidosis. Symptoms of lactic acidosis are non-specific such as feeling or being very sick, vomiting, stomach ache with muscle cramps, a general feeling of not being well with severe tiredness, and difficulty in breathing. Further symptoms are reduced body temperature and heartbeat. **If this happens to you, you may need immediate hospital treatment, as lactic acidosis can lead to coma. Stop taking this**

medicine immediately and contact a doctor or the nearest hospital straight away (see section 2). Take the medicine pack with you.

If you forget to take Jentadueto
If you forget to take a dose, take it as soon as you remember it. However, if it is nearly time for the next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose. Never take two doses at the same time (morning or evening).

If you stop taking Jentadueto
Keep taking Jentadueto until your doctor tells you to stop. This is to help keep your blood sugar under control.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some symptoms need immediate medical attention
You should stop taking Jentadueto and see your doctor straight away if you experience the following symptoms of low blood sugar (hypoglycaemia): trembling, sweating, anxiety, blurred vision, tingling lips, paleness, mood change, or confusion. Hypoglycaemia (frequency very common (may affect more than 1 in 10 people)) is an identified side effect for the combination of Jentadueto plus sulphonylurea and for the combination Jentadueto plus insulin.

Jentadueto may cause a very rare (may affect up to 1 user in 10 000), but very serious side effect called lactic acidosis (see section 'Warnings and precautions'). If this happens you must **stop taking Jentadueto and contact a doctor or the nearest hospital immediately**, as lactic acidosis may lead to coma.

Some patients have experienced inflammation of the pancreas (pancreatitis; frequency rare, may affect up to 1 in 1 000 people).
STOP taking Jentadueto and contact a doctor immediately if you notice any of the following serious side effects:
- Severe and persistent pain in the abdomen (stomach area) which might reach through to your back, as well as nausea and vomiting, as it could be a sign of an inflamed pancreas (pancreatitis).

Other side effects of Jentadueto include:
Some patients have experienced allergic reactions (frequency rare), which may be serious, including wheezing and shortness of breath (bronchial hyperreactivity; frequency uncommon (may affect up to 1 in 100 people)). Some patients experienced rash (frequency uncommon), hives (urticaria; frequency rare), and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing (angioedema; frequency rare). If you experience any of the signs of illness mentioned above, stop taking Jentadueto and call your doctor right away. Your doctor may prescribe a medicine to treat your allergic reaction and a different medicine for your diabetes.

Some patients have had the following side effects while taking Jentadueto:
- Common (may affect up to 1 in 10 people): diarrhoea, blood enzyme increase (lipase increase), feeling sick (nausea)
- Uncommon: inflamed nose or throat (nasopharyngitis), cough, loss of appetite (decreased appetite), being sick (vomiting), blood enzyme increase (amylase increase), itching (pruritus)
- Rare: blistering of skin (bullous pemphigoid)

Some patients have experienced the following side effects while taking Jentadueto with insulin
- Uncommon: liver function disorders, constipation

Side effects when taking metformin alone, that were not described for Jentadueto:
- Very common: abdominal pain.
- Common (may affect up to 1 in 10 people): a metallic taste (taste disturbance), decreased or low vitamin B12 levels in the blood (symptoms may include extreme tiredness (fatigue), a sore and red tongue (glossitis), pins and needles (paraesthesia) or pale or yellow skin). Your doctor may arrange some tests to find out the cause of your symptoms because some of these may also be caused by diabetes or due to other unrelated health problems.
- Very rare (may affect up to 1 in 10 000 people): hepatitis (a problem with your liver), skin reaction as redness of the skin (erythema).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Jentadueto

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister, bottle and carton after EXP. The expiry date refers to the last day of that month.

This medicine 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.

Do not use this medicine if the package is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Jentadueto contains

- The active substances are linagliptin and metformin hydrochloride.
- Each Jentadueto 2.5 mg/850 mg film-coated tablet contains 2.5 mg of linagliptin and 850 mg of metformin hydrochloride.
- Each Jentadueto 2.5 mg/1 000 mg film-coated tablet contains 2.5 mg of linagliptin and 1 000 mg of metformin hydrochloride.
- The other ingredients are:
  - Tablet core: arginine, copovidone, magnesium stearate, maize starch, silica, colloidal anhydrous.
  - Film coating: hypromellose, titanium dioxide (E171), talc, propylene glycol.
    Jentadueto 2.5 mg/850 mg film-coated tablets also contains iron oxide red (E172) and iron oxide yellow (E172).
    Jentadueto 2.5 mg/1 000 mg film-coated tablets also contains iron oxide red (E172).

What Jentadueto looks like and contents of the pack

Jentadueto 2.5 mg/850 mg are oval, biconvex, light orange, film-coated tablets (tablets). They have

“D2/850” debossed on one side and the Boehringer Ingelheim logo debossed on the other.

Jentadueto 2.5 mg/1 000 mg are oval, biconvex light pink film-coated tablets (tablets). They have “D2/1000” debossed on one side and the Boehringer Ingelheim logo debossed on the other.

Jentadueto is available in perforated unit dose blisters with 10 × 1, 14 × 1, 28 × 1, 30 × 1, 56 × 1, 60 × 1, 84 × 1, 90 × 1, 98 × 1, 100 × 1 and 120 × 1 film-coated tablets and multipacks containing 120 × 1 (2 packs of 60 × 1), 180 × 1 (2 packs of 90 × 1), 180 × 1 (3 packs of 60 × 1) and 200 × 1 (2 packs of 100 × 1) film-coated tablets.

Jentadueto is also available in plastic bottles with plastic screw cap and a silica gel desiccant. Bottles contain 14, 60 or 180 film-coated tablets.

Not all pack sizes may be marketed in your country.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.