EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 December 2013
EMA/CHMP/758426/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Jentadueto

International non-proprietary name: linagliptin / metformin

Procedure No. EMEA/H/C/002279/II/0012

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@☐ma.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Boehringer Ingelheim International GmbH submitted to the European Medicines Agency on 9 July 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Jentadueto	linagliptin / metformin	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to add a new indication for the use of Jentadueto in combination with insulin in adult patients with type 2 diabetes when insulin and metformin do not provide adequate glycaemic control. The Package Leaflet was proposed to be updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Rapporteur: Pieter de Graeff

1.2. Steps taken for the assessment

Submission date:	9 July 2013
Start of procedure:	26 July 2013
Rapporteur's preliminary assessment report circulated on:	18 September 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 October 2013
MAH's responses submitted to the CHMP on:	15 November 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	05 December 2013
Rapporteur's final assessment report on the MAH's responses circulated on:	17 December 2013
CHMP opinion:	19 December 2013

2. Scientific discussion

2.1. Introduction

In August 2011, linagliptin (Trajenta) film-coated tablets 5 mg were approved in the European Union (EU/1/11/707) for the treatment of adult patients with type 2 diabetes mellitus. Approval of an indication extension was granted in October 2012 for the use of linagliptin in combination with insulin when insulin and metformin do not provide adequate glycaemic control.

In July 2012, a fixed-dose combination of linagliptin and metformin (Jentadueto) film-coated tablets (2.5 mg linagliptin / 850 mg metformin bid and 2.5 mg linagliptin / 1000 mg metformin bid) was approved in the European Union (EU/1/12/780) for the treatment of adult patients with type 2 diabetes mellitus. The approval was granted for the fixed-dose combination of linagliptin and metformin in patients inadequately controlled on their maximal tolerated dose of metformin alone or in patients already treated with linagliptin and metformin. The fixed-dose combination of linagliptin and metformin is additionally indicated as combination therapy with a sulphonylurea in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.

With the present submission, the Marketing Authorisation Holder (MAH) is applying for the use of Jentadueto as combination therapy with insulin in adult patients with type 2 diabetes when insulin and metformin do not provide adequate glycaemic control.

2.2. Clinical Efficacy aspects

The MAH has based its proof of efficacy for this application on the results of 2 phase III clinical trials (1218.36 and 1218.63).

The proof of efficacy is primarily based on a subset of patients from the pivotal placebo-controlled trial 1218.36, in which linagliptin was investigated in addition to a background of basal insulin therapy with or without oral antidiabetic drugs. Further proof of efficacy is provided by the supportive trial 1218.63, in which linagliptin was investigated in elderly patients; this trial included a subset of patients taking insulin and metformin as background therapy. The efficacy of the triple combination of linagliptin, metformin, and insulin is compared with the combination of placebo, metformin, and insulin.

An interim report of trial 1218.36 was submitted to the EMA as part of a type II variation to extend the indication of Trajenta (linagliptin) to include add-on to insulin. The final study report of 1218.36 has been submitted to the EMA within the current application. The final study report for trial 1218.63 was submitted to the EMA with the responses to Day 120 questions during the initial Marketing Authorisation (MA) evaluation for Jentadueto.

Both trials were arranged into two relevant efficacy groupings (EFF 1 and EFF-2) and include subsets of patients who were treated with both metformin and insulin as background therapy (table 1)

The principal proof of efficacy of the triple combination of linagliptin, metformin, and insulin is based on EFF-1, which comprises a subset of patients from the pivotal placebo-controlled trial 1218.36, which investigated the efficacy of linagliptin versus placebo as add-on therapy to basal insulin with or without oral antidiabetic drugs. All patients from trial 1218.36 who were taking both metformin and insulin as background therapy (comprising 82.9% of patients in 1218.36) are included in EFF-1. The primary endpoint was the HbA1c change from baseline after 24 weeks; efficacy was also investigated over the entire study duration of at least 52 weeks.

Efficacy in elderly patients is based on EFF-2, which comprises a pooling of elderly patients (≥ 70 years) from trials 1218.36 (insulin add-on trial) and 1218.63 (trial conducted in elderly patients) who were taking both metformin and insulin as background therapy. The primary endpoint was the HbA1c change from baseline after 24 weeks.

Table 1: Grouping of studies for the evaluation of efficacy

Shorthand	Characteristics and objective of study grouping	Trial
EFF-1	Pivotal double-blind, placebo-controlled, efficacy trial with basal insulin background with or without oral antidiabetic drugs (OADs) to determine the efficacy of linagliptin 5mg + metformin vs. placebo + metformin as add on to insulin with or without other OADs	1218.36 [1]
EFF-2	Double-blind, placebo-controlled efficacy trials in elderly patients with insulin background with or without oral antidiabetic drugs (pooled) to determine the efficacy of linagliptin 5mg + metformin vs. placebo + metformin as add on to insulin with or without other OADs in elderly patients (age ≥ 70 years)	1218.36 [1,2] 1218.63 [1]

[1] Only patients taking background both metformin and insulin as background therapy are included
[2] Only patients aged at least 70 years are included

A summary of both efficacy groupings is shown in ***Table 2*** below. The vast majority of the treated patients had a baseline HbA1c measurement and at least one on-treatment HbA1c measurement and patients were therefore included in the Full Analysis Set (FAS), the analysis set used for the efficacy analyses. Some patients could be included in both efficacy groupings (i.e. patients from trial 1218.36 who were aged 70 years or more and were taking both insulin and metformin as background medication).

Table 2: Number of patients included in the efficacy study groupings

			Patients included in efficacy grouping, N (%) [1]					
			Treated			FAS		
Grouping	Trial	Patients treated in trial, N	Total	Pbo+ Met+Ins	Lina+ Met+Ins	Total	Pbo+ Met+Ins	Lina+ Met+Ins
EFF-1 [2]	1218.36	1255 [3]	1040 (82.9)	517 (41.2)	523 (41.7)	1021 (81.4)	506 (40.3)	515 (41.0)
EFF-2 [4]	1218.36	1255 [3]	149 (11.9)	80 (6.4)	69 (5.5)	147 (11.7)	78 (6.2)	69 (5.5)
	1218.63	241	36 (14.9)	12 (5.0)	24 (10.0)	36 (14.9)	12 (5.0)	24 (10.0)
	Total	1496	185 (12.4)	92 (6.1)	93 (6.2)	183 (12.2)	90 (6.0)	93 (6.2)

Pbo = placebo study treatment; Lina = linagliptin study treatment; Met = metformin background therapy; Ins = insulin background therapy

[1] Percentages refer to the overall number of patients treated within the respective trials
[2] Only patients who received both metformin and insulin background therapy are included in this grouping
[3] This total is 6 patients fewer than stated in the clinical trial report for 1218.36 because these patients were subsequently excluded from all analyses due to the discovery of serious non-compliance at a study site
[4] Only patients who were aged at least 70 years and who received metformin and insulin background therapy are included in this grouping. The distribution of patient numbers between treatment groups in EFF-2 reflects the 2:1 randomisation ratio (linagliptin:placebo) in trial 1218.63.

Methods

- **Study participants**

Both 1218.36 and 1218.63 trials included male and female patients who had been diagnosed with type 2 diabetes and had insufficient glycaemic control. Due to their specific objectives, the studies differed with respect to their inclusion and exclusion criteria. All patients in 1218.36 had to have a background basal insulin therapy (with or without oral antidiabetic therapy with metformin and/or pioglitazone). The permitted background medication in study 1218.63 included metformin and/or sulphonylurea and/or basal insulin. Patients in both trials completed a 2-week placebo run-in before the first administration of study medication. In study 1218.36, patients had to have a BMI of 45 kg/m² or less, while in 1218.63 no upper limit for BMI was specified. Patients in study 1218.36 had to be a minimum of 18 years old, while patients in study 1218.63 had to be at least 70 years old. In both studies there were no specified requirements with respect to upper limit of age or renal impairment status. The required HbA1c lower limit at screening was 7.0% for both studies, whereas the upper limit was 10.0% in study 1218.36; for study 1218.63 no upper limit was specified.

Trial 1218.36

Trial 1218.36 A Phase III randomised, double-blind, placebo-controlled, parallel-group, efficacy and safety study of linagliptin (5 mg), administered orally once daily for at least 52 weeks in type 2 diabetic patients in combination with basal insulin therapy

Objective: The objective of this trial was to investigate the efficacy and safety of linagliptin 5 mg versus placebo administered for at least 52 weeks as add-on to basal insulin therapy to patients with T2DM and insufficient glycaemic control.

Methods: This was a multicentre, randomised, double-blind, parallel-group, placebocontrolled Phase III study in patients with T2DM. Eligible patients were at least 18 years of age and were being treated with subcutaneous basal insulin alone or in combination with metformin and/or pioglitazone. At screening, glycosylated haemoglobin (HbA1c) was to be 7.0% to 10.0%, and body mass index (BMI) was to be no more than 45 kg/m2. Patients underwent a 2-week placebo run-in period, followed by a randomised, double-blind treatment period of at least 52 weeks. During the first 24 weeks of randomised treatment, the background dose of basal insulin was to remain stable. After that, the dose of basal insulin could be adjusted according to the clinical judgement of the investigator, while the dose of oral antidiabetic drugs (metformin and/or pioglitazone) was to remain stable throughout the whole study.

Endpoints: The primary endpoint was the change from baseline in HbA1c after 24 weeks of treatment. Superiority of linagliptin over placebo was tested using an ANCOVA, with treatment, concomitant oral antidiabetics, and baseline renal function impairment category as fixed classification effects, and baseline HbA1c as covariate. Various sensitivity analyses were performed. Secondary endpoints included the treat-to-target efficacy response (HbA1c <7.0%; HbA1c <6.5%), the relative efficacy response (lowering of HbA1c by at least 0.5%), the change from baseline in HbA1c by visit over time, the change from baseline in fasting plasma glucose (FPG), and the change from baseline in weighted mean daily glucose using the 8- point blood glucose profile. Other efficacy endpoints were the use of rescue therapy, the incidence of asymptomatic hypoglycaemia, and the change in body weight. Safety endpoints included the frequency and intensity of AEs, clinically relevant new or worsening findings in physical examination, 12-lead electrocardiograms, vital signs, and clinical laboratory parameters.

Trial 1218.63

Trial 1218.63 A Phase III randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of linagliptin (5 mg), administered orally once daily over 24 weeks in type 2 diabetic patients (age ≥ 70 years) with insufficient glycaemic control (HbA1c ≥ 7.0%) despite metformin and/or sulphonylurea and/or insulin therapy.

Objective: The objective of this trial was to investigate the efficacy and safety of linagliptin 5 mg once daily versus placebo in elderly patients (≥ 70 years) with type 2 diabetes mellitus (T2DM) for 24 weeks.

Methods: This was a multi-centre, randomised, placebo-controlled, double-blind, parallel group Phase III study in patients with T2DM who were at least 70 years old and had insufficient glycaemic control (glycosylated haemoglobin, HbA1c ≥ 7.0%) despite stable metformin and/or sulphonylurea and/or insulin therapy. Patients who successfully completed the screening period underwent a 2-week open-label placebo run-in period, which was followed by randomised treatment for 24 weeks and a 1-week follow-up period. Doses of background antidiabetic medications were kept stable during screening, run-in, and the first 12 weeks of randomised treatment, after which adjustments were permitted.

Endpoints: The primary endpoint was the change in HbA1c from baseline after 24 weeks of treatment. Superiority of linagliptin over placebo was tested using an ANCOVA with treatment and prior use of insulin as fixed classification effects and baseline HbA1c as linear covariate. Important secondary endpoints were the change from baseline in FPG after 24 weeks, occurrence of the treat-to-target response (HbA1c <7.0% after 24 weeks), and the occurrence of the relative efficacy response (lowering of HbA1c by at least 0.5% after 24 weeks). Safety endpoints included the frequency and intensity of AEs, clinically relevant new or worsening findings in physical examination, 12-lead electrocardiograms, vital signs, and clinical laboratory parameters.

Results

- **Disposition**

For both of the efficacy study groupings, the rate of premature discontinuations up to the timepoint of analysis of the primary endpoint at 24 weeks was less than 10% and was lower in the linagliptin+metformin+insulin group than in the placebo+metformin+insulin group. Disposition in the efficacy study groupings up to 24 weeks, including the main reasons for premature discontinuation, is summarised in **Table 3**.

Table 3: Summary of disposition up to 24 weeks in the efficacy study groupings – FAS

	EFF-1		EFF-2	
	Pbo+ Met+Ins N (%)	Lina+ Met+Ins N (%)	Pbo+ Met+Ins N (%)	Lina+ Met+Ins N (%)
Number of patients	506 (100.0)	515 (100.0)	90 (100.0)	93 (100.0)
Not prematurely discontinued	472 (93.3)	498 (96.7)	82 (91.1)	88 (94.6)
Prematurely discontinued	34 (6.7)	17 (3.3)	8 (8.9)	5 (5.4)
Adverse event	10 (2.0)	7 (1.4)	2 (2.2)	4 (4.3)
Lack of efficacy [1]	4 (0.8)	0 (0.0)	0	0
Administrative reason [2]	13 (2.6)	8 (1.6)	5 (5.6)	1 (1.1)
Other reason	7 (1.4)	2 (0.4)	1 (1.1)	0

Pbo = placebo study treatment; Lina = linagliptin study treatment; Met = metformin background therapy; Ins = insulin background therapy

[1] Includes patients who discontinued due to hyperglycaemia
[2] Non-compliance to study protocol, lost to follow-up, or refusal to continue study medication

- **Baseline data**

Selected demographic data in the efficacy study groupings are summarised in Table 4 below. The demographics were comparable between treatment groups for EFF-1 and EFF-2.

Table 4: Summary of selected demographic data in the efficacy study groupings – FAS

	EFF-1		EFF-2	
	Pbo+ Met+Ins	Lina+ Met+Ins	Pbo+ Met+Ins	Lina+ Met+Ins
Number of patients, N (%)	506 (100.0)	515 (100.0)	90 (100.0)	93 (100.0)
Age, mean (SD) [years]	60.1 (9.6)	59.5 (9.7)	74.0 (3.6)	73.7 (3.7)
BMI, mean (SD) [kg/m^2]	31.3 (4.9)	31.0 (5.4)	30.1 (4.4)	31.0 (5.3)
Male gender, (%)	50.6	51.5	45.6	48.4
Geographic region, (%)				
Europe	48.4	47.6	70.0	65.6
South America [1]	25.5	23.1	10.0	8.6
North America [2]	15.0	16.9	15.6	20.4
Asia	11.1	12.4	4.4	5.4
Race, (%)				
White	82.4	81.0	93.3	93.5
Asian	13.0	14.6	5.6	5.4
Black [3]	4.5	4.5	1.1	1.1

Pbo = placebo study treatment; Lina = linagliptin study treatment; Met = metformin background therapy; Ins = insulin background therapy
[1] Including Mexico
[2] Including New Zealand and Australia
[3] Or African American

The mean HbA_{1c} and FPG values at baseline were similar across efficacy groupings and between the treatment groups. The vast majority of patients in both of the efficacy groupings had been diagnosed with diabetes for more than 5 years. All patients were taking metformin at baseline; less than 10% of patients in each of the efficacy groupings were taking pioglitazone in addition. Sulphonylureas as background medication were not permitted in trial 1218.36, from which all patients in EFF-1 were provided. In EFF-2 (which additionally included patients from trial 1218.63) a total of 9.7% of patients in the linagliptin+metformin+insulin group and none in the placebo+metformin+insulin group were taking a sulphonylurea. Selected baseline characteristics are summarised in the following table.

Table 5: Summary of selected baseline characteristics and oral antidiabetic drugs in the efficacy study groupings – FAS

	EFF-1		EFF-2	
	Pbo+ Met+Ins	Lina+ Met+Ins	Pbo+ Met+Ins	Lina+ Met+Ins
Number of patients, N (%)	506 (100)	515 (100)	90 (100.0)	93 (100.0)
Baseline HbA_{1c}, mean (SD) [%]	8.3 (0.9)	8.3 (0.9)	8.1 (0.8)	8.1 (0.8)
Baseline FPG, mean (SD) [mg/dL]	152.5 (45.0)	147.7 (45.4)	151.9 (46.0)	150.1 (41.1)
Diabetes for >5 years, (%)	87.5	82.5	98.9	93.5
Oral antidiabetic drugs at baseline, (%) [1]				
None	91.5	91.1	93.3	83.9
Pioglitazone	8.5	8.9	6.7	6.5
Sulphonylurea	0	0	0	9.7

Pbo = placebo study treatment; Lina = linagliptin study treatment; Met = metformin background therapy; Ins = insulin background therapy

[1] Does not include metformin, which was taken by all patients

All patients included in the efficacy study groupings for this submission were treated with insulin as background therapy. A prerequisite for participation in trial 1218.36, which provided patients to EFF-1, was that patients were treated with basal insulin. Almost half of the patients in EFF-1 (48.6%) were taking insulin glargine as their basal insulin therapy, whereas 31.4% were taking Neutral Protamine Hagedorn (NPH) insulin and 20.0% were taking insulin detemir. The mean daily basal insulin dose in EFF-1 was 39.7 IU and was similar for both treatment groups. In the grouping of elderly patients (i.e. EFF-2), just over half of the patients (51.9%) were taking insulin glargine, while NPH insulin was taken by 36.1% of patients and insulin detemir was taken by 12.0% of patients. The average mean daily dose of insulin in EFF-2 was 33.7 IU, and was similar in both treatment groups.

- **Change from baseline in HbA1c**

For both of the trials contributing to the evaluation of efficacy in this submission, the primary analysis was based on the change from baseline in HbA_{1c} after 24 weeks of treatment. Because the overall study duration of trial 1218.36 was at least 52 weeks, analyses of efficacy over time up to 52 weeks are additionally presented for EFF-1.

In both efficacy groupings, the triple combination of linagliptin, metformin, and insulin provided clinically meaningful reductions from baseline in HbA_{1c} after 24 weeks compared with the combination of placebo, metformin, and insulin. The adjusted mean treatment differences were -0.68% for patients from the pivotal trial (EFF-1) and -0.81% for the elderly patients (EFF-2) (Table 6).

Table 6: Change from baseline in HbA1c [%] after 24 weeks in the efficacy groupings – FAS (LOCF)

Study grouping/ Treatment group	Number of patients, N (%)	HbA_{1c} baseline, mean (SD)	Change in HbA_{1c} from baseline		Difference to Pbo+Met+Ins		
			Mean (SD)	Adjusted [1] mean (SE)	Adjusted [1] mean (SE)	95% CI	p-value
EFF-1/							
Pbo+Met+Ins	506 (49.6)	8.28 (0.85)	0.03 (0.92)	-0.10 (0.06)			
Lina+Met+Ins	515 (50.4)	8.28 (0.86)	-0.65 (0.88)	-0.77 (0.06)	-0.68 (0.05)	(-0.78, -0.57)	<0.0001

EFF-2/							
Pbo+Met+Ins	90 (49.2)	8.14 (0.81)	0.08 (0.75)	0.12 (0.10)			
Lina+Met+Ins	93 (50.8)	8.13 (0.84)	-0.73 (0.67)	-0.69 (0.09)	-0.81 (0.10)	(-1.01, -0.61)	<0.0001

Pbo = placebo study treatment; Lina = linagliptin study treatment; Met = metformin background therapy; Ins = insulin background therapy

[1] ANCOVA model includes continuous baseline HbA_{1c}, renal impairment category, treatment, and concomitant oral antidiabetic drugs

Because the duration of pivotal trial 1218.36 was at least 52 weeks, changes from baseline in HbA_{1c} after 52 weeks and over time were analysed for the patients from this trial (EFF-1). This analysis showed that the difference between treatment groups in terms of adjusted mean change from baseline in HbA_{1c} increased up to 18 weeks and was sustained up to 24 weeks. After 24 weeks, when the investigators could adjust the prescribed basal insulin dose, the difference between treatment groups remained similar and was still clinically relevant; at 52 weeks, the adjusted mean treatment difference was -0.58% (95% CI: -0.69, -0.47; p<0.0001) (Figure 1).

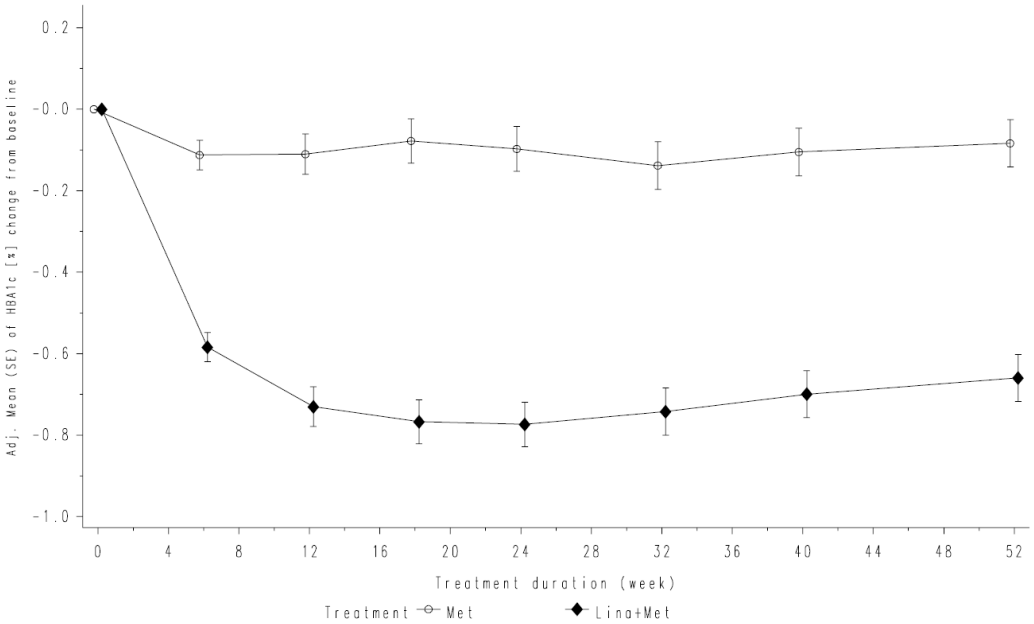

Figure 1: Adjusted mean change in HbA1c [%] and SE from baseline to 52 weeks of treatment in EFF-1 – FAS (LOCF)

Met=Placebo+Metformin+Insulin; Lina+Met= Linagliptin+Metformin+Insulin

Other efficacy endpoints

Proportions of patients achieving HbA1c below 7.0% or HbA1c lowering by at least 0.5%

Of the patients from the pivotal trial 1218.36 (EFF-1) who had baseline HbA_{1c} of 7.0% or greater, 21.2% of those in the linagliptin+metformin+insulin group and 8.4% of those in the placebo+metformin+insulin group achieved HbA_{1c} values of less than 7.0% after 24 weeks of treatment. After 52 weeks, which included the time during which the insulin dose could be adjusted, 17.0% of the patients in the linagliptin+metformin+insulin group and 6.4% of the patients in the placebo+metformin+insulin group achieved HbA_{1c} values of less than 7.0%. The proportion of patients that had a reduction in HbA_{1c} of at least 0.5% after 24 weeks was higher in the linagliptin+metformin+insulin group (56.5%) than in the placebo+metformin+insulin group (22.5%). After 52 weeks, 40.0% of the patients in the

linagliptin+metformin+insulin group and 17.0% of the patients in the placebo+metformin+insulin group achieved HbA_{1c} reductions of at least 0.5%.

Of the elderly patients (EFF-2) who had baseline HbA_{1c} of 7.0% or greater, 30.0% of those in the linagliptin+metformin+insulin group and 6.9% of those in the placebo+metformin+insulin group achieved HbA_{1c} values of less than 7.0% after 24 weeks of treatment. The proportion of patients that had a reduction in HbA_{1c} of at least 0.5% after 24 weeks was 62.4% in the linagliptin+metformin+insulin group and 15.6% in the placebo+metformin+insulin group.

Change from baseline in FPG

In EFF-1 (patients taking both metformin and insulin from the placebo-controlled pivotal trial 1218.36), the adjusted mean difference between treatment groups with regard to the FPG change from baseline was 12.5 mg/dL (95% CI: -17.8, -7.2; p<0.0001). For the grouping of elderly patients (EFF-2), the adjusted mean treatment difference was 19.5 mg/dL (95% CI: -33.4, -5.6; p=0.0061), which is in line with the results for HbA1c. These results are consistent with findings from previous trials in the linagliptin development program.

Use of rescue medication

There were slight differences in the definitions of rescue medication in each of the trials contributing patients to the efficacy analysis. In 1218.36, the first choice of rescue medication was the adjustment of basal insulin therapy; any increase in prescribed insulin dose of more than 10% of the baseline dose was regarded as rescue medication. In very rare cases, background therapy could be adjusted or another oral antidiabetic medication could be added as rescue medication. In 1218.63, rescue medication was considered as any addition of an antidiabetic drug or increase in the dose of background medication for more than 7 days.

For the patients from the pivotal trial 1218.36 (EFF 1), 34.4% of patients in the linagliptin+metformin+insulin group required rescue therapy, compared with 48.6% in the placebo+metformin+insulin group. Of the grouping of elderly patients (EFF-2), 6.5% in the linagliptin+metformin+insulin group required rescue medication, compared with 17.8% in the placebo+metformin+insulin group.

Change from baseline in insulin dose

According to the trial protocols, the background insulin dose was to have been maintained at a stable level up to 24 weeks for 1218.36 and 12 weeks for 1218.63. Analysis of the mean changes in insulin dose in the efficacy groupings showed that mean insulin doses were stable up to the timepoints of the primary analysis. For each of the efficacy groupings a smaller proportion of patients in the linagliptin+metformin+insulin group than patients in the placebo+metformin+insulin group had insulin dose increases of more than 10% during the period up to the primary endpoint. For the patients from the placebo-controlled pivotal trial (EFF-1), the changes in insulin dose were analysed over time including the period after 24 weeks during which changes in insulin dose were permitted. During this period, the changes in mean basal insulin dose were greater for patients in the placebo+metformin+insulin group than in the linagliptin+metformin+insulin group; the changes from baseline at 52 weeks were 4.4 IU (from a baseline of 39.2 IU) in the placebo+metformin+insulin group and 2.4 IU (from a baseline of 40.2 IU) in the linagliptin+metformin+insulin group.

Change from baseline in body weight

In each of the efficacy groupings, there were no clinically meaningful effects on body weight in both treatment groups (no more than ±1 kg change in adjusted mean weight from baseline) at the timepoint of the primary analysis at 24 weeks. The changes in body weight from baseline at 52 weeks were

negligible for both treatment groups in EFF 1.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 7: Summary of efficacy for trial 1218.36

BI trial number Report number	Number of study centres / locations Study start and completion	Study design and type of control Main inclusion criteria Key demographic characteristics: age, mean ± SD (range); gender; BMI, mean ± SD (range); baseline HbA_{1c}, mean ± SD (range)	Study & control drugs Dose regimen	Study objective	No. of randomised / completed patients by treatment arm	Planned duration of treatment	Primary endpoint and key secondary endpoint
Pivotal double-blind, placebo-controlled study							
1218.36 interim analysis [U11-2286] final analysis [U12-1511]	167 centres in 19 countries (Argentina, Belgium, Brazil, Canada, Czech Republic, Finland, Germany, Greece, Italy, Korea, Mexico, Netherlands, Norway, Peru, Russia, Slovakia, Spain, Taiwan, United States) Aug-09 to Sep-11 Cut-off date for interim analysis: 12 Feb 2011	Randomised, double-blind, placebo-controlled, parallel-group comparison Patients with T2DM and insufficient glycaemic control being treated with basal insulin alone or in combination with metformin and/or pioglitazone (HbA_{1c} at screening 7.0 to 10.0%); age ≥18 years; BMI ≤45 kg/m² Age: 60.0 ± 10.0 (22 - 91) years Gender: 47.8% female; 52.2% male BMI: 30.97 ± 5.19 (18.1 - 46.9) kg/m² Baseline HbA_{1c}: 8.30 ± 0.85 (5.9 - 11.5)%	Study drug: Linagliptin 5 mg tablet Control drug: Placebo tablet Orally, once daily	To evaluate efficacy and safety of 5 mg linagliptin in comparison with placebo as add-on therapy to basal insulin	Randomised: Total: 1263 Lina: 633 Placebo: 630 Completed: Total: 1063 Lina: 543 Placebo: 520	A 2-week placebo run-in period followed by a double-blind treatment period of at least 52 weeks. The background dose of basal insulin was to remain stable for the first 24 weeks. After the treatment period, there was a 1-week follow-up period.	Primary endpoint: Change from baseline in HbA_{1c} after 24 weeks of treatment Adjusted mean change from baseline in HbA_{1c} (SE) [%]: Linagliptin: -0.58 (0.08) Placebo: 0.07 (0.08) Difference: -0.65 (p<0.0001) Secondary endpoint: Change from baseline in FPG after 24 weeks of treatment Adjusted mean change from baseline in FPG (SE) [mg/dL]: Linagliptin: -7.1 (4.0) Placebo: 4.5 (3.9) Difference: -11.6 (p<0.0001)

Table 8: Summary of efficacy for trial 1218.63

BI trial number Report number	Number of study centres / locations Study start and completion	Study design and type of control Main inclusion criteria Key demographic characteristics: age, mean ± SD (range); gender; BMI, mean ± SD (range); baseline HbA_{1c}, mean ± SD (range)	Study & control drugs Dose regimen	Study objective	No. of randomised / completed patients by treatment arm	Planned duration of treatment	Primary endpoint and key secondary endpoint
Pivotal double-blind, placebo-controlled efficacy study							
1218.63 [U11-1781]	33 centres in 5 countries (Australia, Canada, Denmark, Netherlands, and Sweden) Mar-10 to Jun-11	Randomised, double-blind, placebo-controlled, parallel-group comparison Elderly patients with T2DM and insufficient glycaemic control (HbA_{1c} at screening ≥7.0%) despite treatment with metformin and/or SU and/or insulin; age ≥70 years; Age: 74.9 ± 4.3 (70 - 91) years Gender: 31.5% female; 68.5% male BMI: 29.67 ± 4.67 (18.4 - 48.0) kg/m² Baseline HbA_{1c}: 7.78 ± 0.76 (6.5 - 11.0)%	Study drug: Linagliptin 5 mg tablet Control drug: Placebo tablet Orally, once daily	To investigate the efficacy and safety of linagliptin 5 mg once daily for 24 weeks in elderly patients with T2DM	Randomised: Total: 241 Lina: 162 Placebo: 79 Completed: Total: 220 Lina: 146 Placebo: 74	2-week placebo run-in followed by 24 weeks of treatment and a 1-week follow-up	Primary endpoint: Change from baseline in HbA_{1c} after 24 weeks of treatment Adjusted mean change from baseline in HbA_{1c} (SE) [%]: Linagliptin: -0.61 (0.06) Placebo: 0.04 (0.07) Difference: -0.64 (p<0.0001) Secondary endpoint: Change from baseline in FPG after 24 weeks of treatment Adjusted mean change from baseline in FPG (SE) [mg/dL]: Linagliptin: -10.6 (3.2) Placebo: 10.1 (4.3) Difference: -20.7 (p<0.0001)

2.2.1 Discussion on clinical efficacy

Design and conduct of clinical studies

Linagliptin 5 mg once daily has been approved for the treatment of adult patients with type 2 diabetes mellitus in combination with several other glucose-lowering medicinal products including metformin and basal insulin.

Jentadueto is a combination of linagliptin 2.5 mg and metformin. Because of the twice daily dosing of metformin, the linagliptin 5 mg is divided in two doses of 2.5 mg. Jentadueto twice daily has been approved for the treatment of adult patients with type 2 diabetes mellitus in combination with several other glucose-lowering medicinal products including metformin, but not insulin.

With the present submission, Boehringer Ingelheim is applying for the use of Jentadueto as combination therapy with insulin.

Subgroup analyses of two trials investigating linagliptin 5 mg once daily in combination with metformin and basal insulin were submitted. The methods of these trials have been assessed in previous submissions. The methods of these trials are acceptable.

No clinical data investigating the effect of Jentadueto in combination with insulin were submitted. However, bioequivalence of linagliptin 1 dd 5 mg and linagliptin 2 dd 2.5 mg has been demonstrated previously. The effect of insulin on the bioequivalence of linagliptin 1 dd 5 mg and 2 dd 2.5 mg is not known, but kinetic data from the clinical studies demonstrate that the trough levels of linagliptin in combination with insulin are similar compared to historical data of linagliptin without insulin. These data suggest that there is no important pharmacokinetic interaction between linagliptin and insulin. This is also supported by the fact that linagliptin is known to have only minor interactions with other drugs. In addition, effects of insulin on metabolic and transporter enzymes are considered unlikely.

Efficacy data and additional analyses

Efficacy of linagliptin in combination with basal insulin is acceptable. The triple combination of linagliptin, metformin, and insulin provided clinically meaningful reductions from baseline in HbA1c after 24 weeks compared with the combination of placebo, metformin, and insulin. The adjusted mean treatment differences were -0.68% for patients from the pivotal trial and -0.81% for the elderly patients.

The results of the effects of linagliptin on fasting plasma glucose, the use of rescue medication and the proportions of patients achieving HbA1c targets are in line with the effects on HbA1c. Interestingly, the patients in the placebo+metformin+insulin group needed more insulin than the patients in the linagliptin+metformin+insulin group. The changes in body weight from baseline at 52 weeks were negligible.
There were no important differential treatment effects across the subgroups. As previously noted, in individuals with diabetes duration less than 1 year, the treatment effect of linagliptin was small. However, this is not a major issue, as most patients that will be treated with a combination of linagliptin and insulin will have longer diabetes duration. Efficacy of linagliptin is acceptable for the investigated subgroups.

2.2.2 Conclusions on clinical efficacy

Efficacy of linagliptin 5 mg once daily in combination with basal insulin and metformin has been demonstrated. Due to bioequivalence of linagliptin 5 mg once daily and linagliptin 2.5 mg twice daily, the CHMP considers the efficacy of Jentadueto in combination with insulin acceptable.

2.3 Clinical safety

This application is supported by safety data from three phase III trials: 1218.36, 1218.43, and 1218.63. All studies are randomised, double-blind, placebo-controlled studies investigating linagliptin 5 mg once daily compared with placebo in patients with type 2 diabetes as add-on therapy to a background of basal insulin with or without oral antidiabetic drugs.

For the integrated analysis of safety, data from these trials were pooled in a single safety grouping. This grouping includes data from the subset of patients who were taking metformin and insulin as background medication. In total, 1079 treated patients are included in the safety analysis presented in this document with the main contribution of 1040 patients arising from study 1218.36. Of the treated patients in the safety grouping, 530 patients were in the placebo+metformin+insulin group and 549 patients were in the linagliptin+metformin+insulin group.

Exposure

Planned treatment durations were at least 52 weeks for study 1218.36, 52 weeks for study 1218.43, and 24 weeks for study 1218.63. Hence, nearly all patients included in this analysis were treated for 24 weeks or more (linagliptin+metformin+insulin: 93.6%, placebo+metformin+insulin: 90.9%); the majority of patients was treated for 52 weeks or more (linagliptin+metformin+insulin: 82.3%, placebo+metformin+insulin: 77.7%). As in study 1218.36 treatment beyond Week 52 was allowed, a considerable proportion of patients in the safety grouping was treated for 88 weeks or more (linagliptin+metformin+insulin: 8.4%, placebo+metformin+insulin: 10.6%).

Exposure was generally comparable between the treatment groups; the overall mean (SD) treatment exposure was 433 (141.2) days for the linagliptin+metformin+insulin group and 421 (153.7) days for the placebo+metformin+insulin group, and the total exposure to randomised study medication was 651.3 patient years in the linagliptin+metformin+insulin group and 610.8 patient years in the placebo+metformin+insulin group.

Patient disposition and premature discontinuation

In the safety set, the frequency of patients who prematurely discontinued treatment was lower for the linagliptin+metformin+insulin group (12.6%) than for the placebo+metformin+insulin group (16.8%). Consistently, the most frequent reasons for premature treatment discontinuation were reported more often in the placebo+metformin+insulin group than in the linagliptin+metformin+insulin group; these reasons were the occurrence of adverse events (linagliptin+metformin+insulin: 4.6%, placebo+metformin+insulin: 5.3%), and refusal to continue study medication (linagliptin+metformin+insulin: 2.9%, placebo+metformin+insulin: 4.5%).

Consistent with the overall analysis, for most subgroups analysed, the proportion of patients who prematurely discontinued treatment was lower for the linagliptin+metformin+insulin group than for the placebo+metformin+insulin group; this was consistent for the age categories (≤ 50, 51 to <65, 65 to <75, 75 to <85, ≥ 85 years of age), gender subgroups (male, female), baseline BMI categories (<30, ≥ 30 kg/m2), baseline HbA1c categories (<8.5%, ≥ 8.5%), renal function subgroups (≥ 90, <90 mL/min), and baseline insulin daily dose categories (≤ 40, >40 IU). Exceptions were noted for the subgroup of Black patients (N= 46), where the rate of premature treatment discontinuation was higher in the linagliptin+metformin+insulin group (34.8%) when compared with the placebo+metformin+insulin group (17.4%); the difference arose solely due to 2 patients in the linagliptin+metformin+insulin group who refused to continue trial medication and 2 patients who were lost to follow up. There was no difference between the treatment groups in the frequency of Black patients who discontinued due to adverse events.

Further subgroups with a slightly higher treatment discontinuation rate in the linagliptin+metformin+insulin group than in the placebo+metformin+insulin group were the subgroup of Asian patients, patients from Asia, and patients who were diagnosed with diabetes for more than 1 and up to 5 years.

Adverse events

The analysis of adverse events was based on the concept of treatment-emergent signs and symptoms, i.e. adverse events not present at start of treatment or events present at start of treatment that worsen during treatment in intensity were analysed. All adverse events occurring between first drug intake and up to and including Day 7 after last drug intake were assigned to the randomised treatment. Adverse event analyses are based on the number of patients with adverse events, not the number of adverse events.

The types of the adverse events analysed for the SCS include all adverse events, all adverse events by intensity, investigator-defined drug-related adverse events, adverse events leading to discontinuation of study medication, adverse events leading to death, serious adverse events, other significant adverse events (based on the ICH E3 definition), hypoglycaemic events, and 8 categories of adverse events of special interest.

A summary of adverse events in the safety grouping is presented in Table 9 below. Overall, the proportion of patients with at least one adverse event reported in the on-treatment phase, were comparable between the linagliptin+metformin+insulin group and the placebo+metformin+insulin group. Proportions of patients with severe adverse events, adverse events leading to treatment discontinuation, and investigator-defined hypoglycaemic events were similar in both treatment groups. Serious adverse events were slightly more frequent in the linagliptin+metformin+insulin group than in the placebo+metformin+insulin group. Investigator-defined drug-related adverse events were more common in the placebo+metformin+insulin group when compared with the linagliptin+metformin+insulin group. The proportions of patients with adverse events of special interest (AESIs) were generally low for all types of AESIs; no patient was reported with AESIs defined as pancreatic cancer, thyroid cancer, or thyroid neoplasm (unspecified). The AESI reported with the highest frequency was hepatic adverse events; with a higher frequency in the linagliptin+metformin+insulin group (16 patients [2.9%]) than in the placebo+metformin+insulin group (8 patients [1.5%]). Pancreatitis was reported for 3 patients (0.5%) in the linagliptin+metformin+insulin group and 1 patient (0.2%) in the placebo+metformin+insulin group.

Table 9: Adverse event overall summary for the safety grouping - Treated set

	Pbo + Met + Ins	Lina + Met + Ins
Exposure, mean (SD) [days]	421 (153.7)	433 (141.2)
Number of patients, N (%)	530 (100.0)	549 (100.0)
Patients with any adverse event, N (%)	427 (80.6)	428 (78.0)
Patients with severe adverse events, N (%)	45 (8.5)	40 (7.3)
Patients with investigator-defined drug-related adverse events, N (%)	114 (21.5)	100 (18.2)
Patients with adverse events leading to discontinuation of trial drug, N (%)	25 (4.7)	23 (4.2)
Patients with serious adverse events, N (%)	68 (12.8)	76 (13.8)
Number of patients with investigator-defined hypoglycaemia, N (%)	164 (30.9)	162 (29.5)
Patients with adverse events of special interest [1], N (%)		
Hepatic adverse events	8 (1.5)	16 (2.9)
Hypersensitivity adverse events	7 (1.3)	10 (1.8)
Drug related gastrointestinal adverse reaction	4 (0.8)	7 (1.3)
Renal adverse events	4 (0.8)	3 (0.5)
Pancreatitis	1 (0.2)	3 (0.5)
Thyroid neoplasm (benign)	0 (0.0)	2 (0.4)
Cutaneous skin reactions	0 (0.0)	1 (0.2)

Pbo = placebo study treatment; Lina = linagliptin study treatment; Met = metformin background therapy; Ins = insulin background therapy

[1] For analysis methods of adverse events of special interest, refer to the SCS [Module 2.7.4, Section 1.1.3.1].

Most frequently reported adverse events

In the safety grouping, the most frequently reported adverse events on the MedDRA system organ class (SOC) level with an incidence of more than 20% of patients in a treatment group were metabolism and nutrition disorders, infections and infestations, musculoskeletal and connective tissue disorders, and gastrointestinal disorders. Proportions of patients in each SOC were generally similar in both treatment groups.

Overall, the most frequently reported adverse events on the MedDRA preferred term (PT) level with an incidence of more than 10% in a treatment group were hypoglycaemia (with similar frequencies in both treatment groups), hyperglycaemia (more frequent in the placebo+metformin+insulin group), and nasopharyngitis (with similar frequencies in both treatment groups). All adverse events reported with a frequency of more than 5% in any treatment group are presented in Table 10.

Preferred terms that were noted with a difference in frequency of more than 2% between the linagliptin+metformin+insulin group and the placebo+metformin+insulin group were hyperglycaemia (13.1% vs. 17.4%) and gastroenteritis (2.2% vs. 4.7%).

Table 10: Frequency of patients with adverse events occurring in more than 5% of patients in either treatment group at the preferred term level, sorted by system organ class and frequency in the linagliptin+metformin+insulin group - Treated set

System organ class/ preferred term	Pbo + Met + Ins		Lina + Met + Ins	
	N	(%)	N	(%)
Number of patients	530	(100.0)	549	(100.0)
Total with adverse events	427	(80.6)	428	(78.0)
Gastrointestinal disorders	103	(19.4)	121	(22.0)
Diarrhoea	23	(4.3)	29	(5.3)
Infections and infestations	206	(38.9)	202	(36.8)
Nasopharyngitis	51	(9.6)	60	(10.9)
Upper respiratory tract infection	22	(4.2)	30	(5.5)
Urinary tract infection	34	(6.4)	25	(4.6)
Influenza	27	(5.1)	22	(4.0)
Metabolism and nutrition disorders	245	(46.2)	238	(43.4)
Hypoglycaemia	156	(29.4)	157	(28.6)
Hyperglycaemia	92	(17.4)	72	(13.1)
Musculoskeletal and connective tissue disorders	125	(23.6)	111	(20.2)
Back pain	27	(5.1)	30	(5.5)
Nervous system disorders	81	(15.3)	87	(15.8)
Headache	21	(4.0)	30	(5.5)
Dizziness	17	(3.2)	28	(5.1)
Vascular disorders	42	(7.9)	41	(7.5)
Hypertension	29	(5.5)	23	(4.2)

Pbo = placebo study treatment; Lina = linagliptin study treatment; Met = metformin background therapy; Ins = insulin background therapy

Drug-related adverse events and adverse events leading to discontinuation

Overall, proportions of patients reported with adverse events leading to premature treatment discontinuation were low in the safety grouping and similar between the treatment groups (linagliptin+metformin+insulin: 23 patients [4.2%], placebo+metformin+insulin: 25 patients [4.7%]). Generally, for all SOCs, proportions of patients with adverse events leading to treatment discontinuation were below 1.0% in both treatment groups; except for the SOC gastrointestinal disorders, which was reported for more patients in the placebo+metformin+insulin group (7 patients [1.3%]) than in the linagliptin+metformin+insulin group (3 patients [0.5%]). Only a few preferred terms were reported by 2 patients in a treatment group. There was no indication that treatment with linagliptin on a background of metformin and insulin increased the rate of adverse events leading to premature discontinuation when compared with placebo treatment on a background of metformin and insulin.

The proportion of patients with investigator-defined drug-related adverse events in the safety grouping was higher in the placebo+metformin+insulin group (21.5%) than in the linagliptin+metformin+insulin group (18.2%). The SOC most frequently reported for investigator-defined drug-related adverse events was metabolism and nutrition disorders (linagliptin+metformin+insulin: 13.3%, placebo+metformin+insulin: 15.1%). The most frequently reported drug-related adverse event at PT level was hypoglycaemia with a higher frequency in the placebo+metformin+insulin group (75 patients [14.2%]) than in the linagliptin+metformin+insulin group (69 patients [12.6%]). Hence, treatment with linagliptin compared with placebo on a background of metformin and insulin did not increase the incidence of drug-related adverse events in the investigated patient population.

Serious adverse events and deaths

Of the 1079 treated patients in this safety analysis, 6 patients died; 3 patients were in the linagliptin+metformin+insulin group, 3 patients were in the placebo+metformin+insulin group. All fatal events were reported in study 1218.36, which contributed most patients to the safety grouping (1040 of 1079 treated patients). Of the patients in the linagliptin+metformin+insulin group who died, 2 patients were reported with sudden death, 1 patient with myocardial infarction. Of the patients in the placebo+metformin+insulin group who died, 2 patients were reported with non-small cell lung cancer, and 1 patient was reported with acute renal failure. All patients died in the on-treatment period. None of the events was considered related to trial medication. The incidence rates per 100 patient years were similar in the treatment groups: 4.53 for the linagliptin+metformin+insulin group and 4.83 for the placebo+metformin+insulin group.

Overall, in the analysed patient population, the frequency of serious adverse events (including fatal adverse events) was low. In the linagliptin+metformin+insulin group 13.8% of patients and 12.8% of patients in the placebo+metformin+insulin group were reported with serious adverse events. The SOC with the highest frequency of serious adverse events was cardiac disorders, reported for similar frequencies of patients in both treatment groups (linagliptin+metformin+insulin: 2.9%, placebo+metformin+insulin: 2.8%). On the PT level, no event was reported with a frequency of more than 1.0% .

Based on preferred terms, serious adverse events with an incidence of more than 0.2% (i.e. 1 or more patients) in either treatment group and reported for more patients in the linagliptin+metformin+insulin group than the placebo+metformin+insulin group were angina unstable (0.5% vs. 0.2%), acute myocardial infarction (0.4% vs. 0.0%), cataract (0.4% vs. 0.0%), gastric ulcer (0.4% vs. 0.2%), sudden death (0.4% vs. 0.0%), bronchitis (0.4% vs. 0.0%), fall (0.5% vs. 0.4%), contusion (0.4% vs. 0.0%), ligament sprain (0.4% vs. 0.2%), road traffic accident (0.4% vs. 0.2%), hypoglycaemia (0.4% vs. 0.0%), ovarian adenoma (0.4% vs. 0.2%), and nephrolithiasis (0.4% vs. 0.0%).

Adverse events of special interest

Hypoglycaemia

The frequency of reported on-treatment hypoglycaemic events was similar in both treatment groups, ranging from 29.1% to 30.9% of patients. Consistently, similar proportions of patients were reported with investigator-defined hypoglycaemic events in both treatment groups irrespective of severity and also for severe hypoglycaemic events, i.e. those requiring assistance (linagliptin+metformin+insulin: 1.5%, placebo+metformin+insulin: 0.9%).

In the study which contributed the majority of patients to this safety analysis (1218.36), hypoglycaemic events were analysed and compared for the first 24 weeks of treatment, where the basal insulin dose was to remain stable, and for the following period up to the end of treatment, where the basal insulin dose could be adjusted. Overall, there was no difference between the placebo and linagliptin treatment groups for the proportion of patients with investigator-reported hypoglycaemic events up to Week 24 and after Week 24 to the end of treatment.

Other adverse events of special interest

Overall, proportions of patients with adverse events of special interest were low for all types of adverse events of special interest. No patients were reported with pancreatic cancer, thyroid cancer, or thyroid

neoplasm (unspecified). The adverse events of special interest reported with the highest frequency was hepatic adverse events; the frequency was higher in the linagliptin+metformin+insulin group (2.9%) when compared with the placebo+metformin+insulin group (1.5%). Also slightly more patients in the linagliptin+metformin+insulin group than in the placebo+metformin+insulin group were reported with hypersensitivity adverse events (1.8% vs.1.3%) mainly due to urticaria (0.7% vs. 0.2%), drug-related gastrointestinal adverse reaction (1.3% vs. 0.8%) mainly due to nausea (1.1% vs. 0.4%), thyroid neoplasm (benign) (0.4% vs. 0.0%), and cutaneous skin reactions (0.2% vs. 0.0%). Renal adverse events were reported by more patients in the placebo+metformin+insulin group compared to the linagliptin+metformin+insulin group (0.8% vs. 0.5%.).

In the safety grouping, 4 patients were reported with pancreatitis. Three of those patients were treated with linagliptin+metformin+insulin, two of which required hospitalisation due to the event; none of the events was reported as having a severe intensity. One patient in the placebo+metformin+insulin group was reported with severe pancreatitis and required hospitalisation due to the event. None of the cases were fatal, necrotising, or haemorrhagic.

Cardiovascular safety

The number of patients who were analysed for the primary endpoint in this meta-analysis were 5847 patients treated with linagliptin, 2675 patients treated with placebo, and 937 patients treated with an active comparator. The primary composite endpoint was composed of the adjudicated events CV death, non-fatal myocardial ischaemia (MI), non-fatal stroke, and hospitalisation due to unstable angina. For the primary endpoint, incidence event rates (per 1000 years of exposure) were 13.4 for linagliptin and 18.9 for the total comparators. For the secondary endpoint 'all adjudicated events', incidence event rates were 21.5 for linagliptin and 29.1 for the combined comparators; for the 'FDA custom MACE' incidence event rates were 8.7 for linagliptin and 13.7 for the combined comparators; and for 'CV death, MI and stroke', incidence event rates were 9.3 for linagliptin and 14.0 for the combined comparators.

The subgroup analyses of the primary endpoint revealed an incidence rate of 29.8 for linagliptin and 27.5 for all comparators for patients on insulin background, of 10.9 for linagliptin and 16.3 for all comparators for patients on metformin background, and 21.3 for linagliptin and 16.2 for all comparators for patients on metformin and insulin background. For the safety analysis in this application, the primary composite cardiovascular endpoint as defined for the meta-analysis was analysed. Of the 549 treated patients in the linagliptin+metformin+insulin group, 14 patients (2.6%) had CEC-confirmed events as defined by this endpoint; giving rise to an incidence rate of 21.3 patients with events per 1000 patient years (PY) at risk. Of the 530 treated patients in the placebo+metformin+insulin group, 10 patients (1.9%) had such events, leading to an incidence rate of 16.2/1000 PY.

A second endpoint was analysed for this application based on FDA custom MACE events. For this endpoint, number of patients with events and incidence rates were similar in the treatment groups: in the linagliptin+metformin+insulin group, 6 patients (1.1%) were reported with such events (incidence rate: 9.1/1000 PY); in the placebo+metformin+insulin group, 5 patients were reported with such events (incidence rate: 8.1/1000 PY).

Laboratory findings and vital signs

In the safety grouping, no clinically meaningful changes from baseline or clinically meaningful differences between the treatment groups were observed for haematology parameters, electrolytes, enzymes, substrates, and urinalysis parameters. There were changes in mean (SD) amylase values; they increased from baseline by 5 (20) U/L in the linagliptin+metformin+insulin group until the end of treatment, whereas in the placebo+metformin+insulin group a change by -1 (21) U/L was noted. Furthermore, for

amylase a higher proportion of patients in the linagliptin+metformin+insulin group (4.5%) than in the placebo+metformin+insulin group (2.9%) shifted from normal values at baseline to high values at the end of treatment. Analyses for possibly clinically significant abnormalities of increased amylase confirmed the above mentioned findings, with more patients in the linagliptin+metformin+insulin group (5.6%) than in the placebo+metformin+insulin group (3.3%).

Only few patients were reported with any of the pre-specified criteria for liver enzyme elevations, most commonly they were from the placebo+metformin+insulin group. One patient in the placebo+metformin+insulin group and no patient in the linagliptin+metformin+insulin group had a lab constellation consistent with potential Hy's law. Mean changes from baseline to last value on treatment were small for all liver enzymes analysed; no relevant differences were noted for the treatment groups. However, shifts from low or normal values at baseline towards high values at the end of treatment were more common in the linagliptin+metformin+insulin group than in the placebo+metformin+insulin group for AST (5.8% vs. 2.7%) and ALT (4.6% vs. 3.2%).

Changes in renal function were evaluated by categorising the estimated creatinine clearance rate (eCcr) based on the Cockcroft-Gault formula. Patients were categorised as having normal renal function (eCcr $\geq$ 90 mL/min), mild renal impairment (eCcr 60 to <90 mL/min), moderate renal impairment (eCcr 30 to <60 mL/min), severe renal impairment (eCcr 15 to <30 mL/min), or end-stage renal disease (eCcr <15 mL/min) at baseline and at the end of treatment.

An analysis over time performed for patients from trial 1218.36 only (i.e. the majority [96%] of patients in the pooled safety analysis) showed a greater reduction in mean eCCR over time in the linagliptin+metformin+insulin group than in the placebo+metformin+insulin group, however, this difference disappeared after adjustment for changes in weight. 35 patients (10.5%) in the linagliptin+metformin+insulin group and 29 patients (8.8%) in the placebo+metformin+insulin group shifted from normal values at baseline to microalbuminuria at the end of treatment: 12 patients (7.8%) in the linagliptin+metformin+insulin group and 9 patients (6.7%) in the placebo+metformin+insulin group shifted from microalbuminuria at baseline to macroalbuminuria at the end of treatment; 3 patients (0.9%) in the linagliptin+metformin+insulin group and 2 patients (0.6%) in the placebo+metformin+insulin group shifted from normal values at baseline to macroalbuminuria at the end of treatment. However, the differences were small and statistical comparisons of the number of patients with deteriorations by means of the Chi-square test did not reveal any indication for a difference between treatment groups (p=0.44 for last value on treatment, p=0.95 for worst value on treatment).

When observing timepoints beyond Week 18 until Week 91, for patients from study 1218.36 only, mean SBP slightly decreased (by a maximum of -3.2 mmHg from baseline at Week 65) in the linagliptin+metformin+insulin group, whereas mean SBP slightly increased towards the end of the treatment (by a maximum of 2.9 mmHg from baseline at Week 91) in the placebo+metformin+insulin group. Mean changes in DBP and pulse rate from baseline until the end of treatment were negligible in both treatment groups.

Post marketing experience

The overall cumulative marketed patient exposure to Jentadueto is estimated to be 9008 PY for the time period 30 Jan 2012 to 31 Dec 2012. The first Periodic Safety Update Report (PSUR) for Jentadueto covers a reporting interval of 20 Jul 2012 to 19 Jan 2013. The interval patient exposure was estimated to be 6740 patient years.

In total, 46 cases (confirmed by healthcare professionals and non-confirmed cases) were reported, of which 3 cases were serious and 43 cases were non-serious. None of the cases were assessed as requiring a change to the safety profile as described in the company core data sheet (CCDS dated 14 December

2012). The majority of the non-serious cases appeared to describe listed adverse events such as gastrointestinal upset, rash, or cough, or events that are associated with diabetes such as hypoglycaemia and peripheral neuropathy. The serious cases were one case of lactic acidosis, one poorly reported case of hypokalaemia, and one case of rhabdomyolysis in a patient with concomitant simvastatin medication. Overall, no case of pancreatitis was reported from spontaneous sources until datalock point of the PSUR.

2.3.1. Discussion on clinical safety

The safety of Jentadueto in combination with basal insulin appears comparable to the safety of linagliptin in combination with metformin and basal insulin.
The frequency of patients who prematurely discontinued treatment was lower for the linagliptin+metformin+insulin group (12.6%) than for the placebo+metformin+insulin group (16.8%). Demographic data were generally balanced across the two treatment groups. Overall, the proportion of patients with at least one adverse event reported in the on-treatment phase, were comparable between the linagliptin+metformin+insulin group and the placebo+metformin+insulin group (78.0% vs. 80.6%). Proportions of patients with severe adverse events and adverse events leading to treatment discontinuation were similar in both treatment groups (7.3% vs. 8.5% and 4.2% vs. 4.7%, respectively). Serious adverse events were slightly more frequent in the linagliptin+metformin+insulin group than in the placebo+metformin+insulin group (13.8% vs. 12.8%). There were no relevant differences in proportions of patients reported with adverse events leading to premature treatment discontinuation.

There was no evidence that treatment with linagliptin compared with placebo in patients with metformin and basal insulin background led to an increase in hypoglycaemic events.

The frequency of hepatic adverse events was slightly higher in the linagliptin+metformin+insulin group (2.9%) when compared with the placebo+metformin+insulin group (1.5%). The side effect hepatic events is stated in the SmPC. Also slightly more patients in the linagliptin+metformin+insulin group than in the placebo+metformin+insulin group were reported with hypersensitivity adverse events (1.8% vs.1.3%). Hypersensitivity adverse events have already been mentioned in the SmPC.

There was an increased risk of pancreatitis, but this risk is in line with previous findings with linagliptin (and other DPP-4 inhibitors) and is listed in the SmPC of Jentadueto.

Compared to the combination of placebo and active comparator on a background of metformin and insulin, cardiovascular events in the group of patients treated with linagliptin were slightly increased (2.6% vs. 1.9%). However, the absolute number of events was low and results are considered inconclusive. Further data from the ongoing cardiovascular outcome study (study 1218.74) is awaited.

An analysis over time performed for patients from trial 1218.36 only (i.e. the majority [96%] of patients in the pooled safety analysis) showed a greater reduction in mean eCCR over time in the linagliptin+metformin+insulin group than in the placebo+metformin+insulin group, however, this difference disappeared after adjustment for changes in weight. There were differences in deteriorations of microalbuminuria**,** However, the differences were small and statistical comparisons of the number of patients with deteriorations by means of the Chi-square test did not reveal any indication for a difference between treatment groups (p=0.44 for last value on treatment, p=0.95 for worst value on treatment).

There was a small decrease in SBP with linagliptin compared to placebo. DBP and pulse were similar.

The majority of the non-serious postmarketing cases appeared to describe listed adverse events. The serious post marketing cases were rare and for now no conclusions can be drawn.

There were several differences in the risk of adverse events in different subgroups: in some subgroups linagliptin was associated with a higher risk of adverse events, whereas in other subgroups placebo was associated with a higher risk. These differences are likely to be due to numerical imbalances.

2.3.2. Conclusions on clinical safety

The safety of Jentadueto in combination with basal insulin appears comparable to the safety of linagliptin in combination with metformin and insulin. However, an increased risk of hepatic events cannot be excluded. The side effect hepatic events has been therefore included in the SmPC.

2.3. Risk management plan

2.3.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

Based on the PRAC review of the Risk Management Plan, version 8.0, dated 13 November 2013 the PRAC considers by consensus that the risk management system for Linagliptin+metformin (Jentadueto) in the treatment of approved indication is acceptable.

Advice on conditions of the marketing authorisation

The PRAC do not advise any changes to the current conditions of the Marketing Authorisation.

Risk management Plan (RMP)

The 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.

Additional risk minimisation measures

The PRAC considers that the existing conditions in the MA relating to additional risk minimisation measures are sufficient.

Obligation to conduct post-authorisation measures

Not applicable

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 11. Summary of the Safety Concerns

Important identified risks	Hypoglycaemia
	Pancreatitis
	Lactic acidosis
	Angioedema/urticaria
	Hypersensitivity reactions
Important potential risks	Skin lesions
	Infections
	Worsening of renal function
Missing information	Paediatric patients (incl. paediatric off-label use)
	Elderly patients >80 years
	Pregnancy/breast-feeding
	Patients with recent cardiovascular events
	Malignancies
	Concomitant therapy with P-glycoprotein (P-gp) and cytochrome P450 (CYP) 3A4 inhibitors
	Use in combinations not studied or approved
	Idiosyncratic reactions
	Immunological adverse reactions

The PRAC agreed.

Pharmacovigilance plan

The table below reflects the ongoing and planned studies in the PhV development plan

Study/activity[1]	Objectives	Safety concerns addressed	Status[2]	Date for submission of interim or final reports[3]
Long term CV-safety study 1218.74 A multicentre, international, randomised, parallel group, double blind study to evaluate CV safety of linagliptin versus glimepiride in patients with T2DM at high CV risk (Phase III interventional study, category 3)	To evaluate CV safety of linagliptin versus glimepiride	• Hypoglycaemia • Pancreatitis • Worsening of renal function • Patients with recent CV events	Ongoing	Event driven Interim analysis Jun 2014 Final analysis Dec 2018
CV safety study 1218.22 A multicenter, international, randomised, parallel group, double-blind, placebo-controlled, cardiovascular safety and renal microvascular outcome study with linagliptin, 5 mg once daily in patients with type 2 diabetes mellitus at high vascular risk (Phase IV interventional study, category 3)	CV outcome study in patients with T2DM at high vascular risk	• Hypoglycaemia • Pancreatitis • Worsening of renal function • Patients with recent CV events	Ongoing	Event driven Final analysis Nov 2019

[1] Type, title and category (1-3).
[2] Planned or started.
[3] Planned or actual.

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures for Jentadueto

Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Hypoglycaemia	Routine pharmacovigilance activities Appropriate labelling in SmPC sections 4.2 Posology, 4.4 Special warnings and precautions, and 4.8 Undesirable effects.	Not applicable
Pancreatitis	Routine pharmacovigilance activities Appropriate labelling in SmPC sections 4.4 Special warnings and precautions and 4.8 Undesirable effects.	Not applicable
Lactic acidosis	Routine pharmacovigilance activities Appropriate labelling in SmPC sections 4.2 Posology, 4.3 Contraindications, 4.4 Special warnings and precautions, 4.5 Interactions, 4.8 Undesirable effects, and 4.9 Overdose.	Not applicable
Angioedema/urticaria	Routine pharmacovigilance activities Appropriate labelling in SmPC sections 4.3 Contraindications and 4.8 Undesirable effects.	Not applicable
Hypersensitivity reactions	Routine pharmacovigilance activities Appropriate labelling in SmPC sections 4.3 Contraindication and 4.8 Undesirable effects.	Not applicable
Important potential risks		
Skin lesions	Routine pharmacovigilance activities Appropriate labelling in SmPC section 4.8 Undesirable effects of the listed adverse reactions of rash for linagliptin and skin reactions such as erythema and urticaria for metformin.	Not applicable
Infections	Routine pharmacovigilance activities Appropriate labelling in SmPC section 4.8 Undesirable effects for the listed reaction of nasopharyngitis.	Not applicable
Worsening of renal function	Routine pharmacovigilance activities	Not applicable

Missing information		
Paediatric patients	Routine pharmacovigilance activities Appropriate labelling in SmPC section 4.2 Posology	Not applicable
Elderly patients <80 years	Routine pharmacovigilance activities Appropriate labelling in SmPC sections 4.2 Posology and 4.4 Special warnings and precautions	Not applicable
Pregnancy/breast-feeding	Routine pharmacovigilance activities Appropriate labelling in SmPC section 4.6 Pregnancy and lactation	Not applicable
Safety in high risk patients with recent cardiovascular events	Routine pharmacovigilance activities Appropriate labelling in SmPC section 4.3 Contraindications	Not applicable
Malignancies	None proposed	Not applicable
Concomitant therapy with P-gp and CYP3A4 inhibitors	Routine pharmacovigilance activities Appropriate labelling in SmPC section 4.5 Interactions	Not applicable
Use in combinations not studied	Routine pharmacovigilance activities Appropriate labelling in SmPC section 4.5 Interactions	Not applicable
Idiosyncratic reactions	Routine pharmacovigilance activities	Not applicable
Immunological adverse reactions	Routine pharmacovigilance activities Appropriate labelling in SmPC sections 4.3 Contraindication and 4.8 Undesirable effects.	Not applicable

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

The CHMP endorsed this advice without changes.

2.4. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed:

Summary of Product Characteristics (SmPC)

4.1 Therapeutic indications

"Jentadueto is indicated in combination with insulin (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in adult patients when insulin and metformin alone do not provide adequate glycaemic control."

4.2 Posology and method of administration

"For 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)."

4.4 Special warnings and precautions for use

"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)."

"~~Use of Jentadueto in combination with insulin~~
~~The use of Jentadueto in combination with insulin has not been adequately studied.~~"

4.8 Undesirable effects

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

"*Adverse reactions reported when linagliptin and metformin were combined with insulin*
When linagliptin and metformin were administered in combination with insulin, constipation was identified as an additional adverse reaction under these conditions. The combination of linagliptin and metformin when administered in combination with insulin may be associated with an increased risk of hepatic events."

" Table 3 Adverse reactions additionally reported in patients when linagliptin and metformin were combined with insulin*:

System organ class Adverse reaction	**Adverse reactions by treatment regimen linagliptin plus metformin plus insulin**
Gastrointestinal disorders	
Constipation	uncommon
Hepatobiliary disorders	
*Liver function disorders**	*common***

* Refer to Summary of Product Characteristics for insulin and metformin for additional information
** *This frequency is calculated from a pooled dataset of 549 patients*"

"Table 4 Adverse reactions reported in patients who received metformin* as monotherapy and that were not observed in patients receiving Jentadueto

System organ class Adverse reaction	**Adverse reactions by treatment regimen metformin monotherapy**
Metabolism and nutrition disorders	
Lactic acidosis	very rare
Vitamin B12 deficiency	very rare
Nervous system disorder	
Taste disturbance	common
Gastrointestinal disorders	
Abdominal pain	very common
Hepatobiliary disorders	
~~Liver function disorders~~ *hepatitis*	very rare
Skin and subcutaneous tissue disorders	
Skin reactions such as erythema, urticaria	very rare

* Refer to Summary of Product Characteristics for metformin for additional information"

5.1 Pharmacodynamic properties

"*Linagliptin in combination with metformin and insulin*
A 24-week placebo-controlled study was conducted to evaluate the efficacy and safety of linagliptin (5 mg once daily) added to insulin with or without metformin. 83% of patients were taking metformin in combination with insulin in this trial. Linagliptin in combination with metformin plus insulin provided significant improvements in HbA1c in this subgroup with -0.68% (CI: -0.78; -0,57) adjusted mean change from baseline (mean baseline HbA1c 8.28%) compared to placebo in combination with metformin plus insulin. There was no meaningful change from baseline in body weight in either group."

"In a pooled analysis of elderly (age ≥ 70 years) patients with type 2 diabetes (n=183) who were taking both metformin and basal insulin as background therapy, linagliptin in combination with metformin plus insulin provided significant improvements in HbA1c parameters with -0.81% (CI: -1.01; -0.61) adjusted mean change from baseline (mean baseline HbA1c 8.13%) compared to placebo in combination with metformin plus insulin"

The Package leaflet was updated to reflect the new indication in combination with insulin.

3. Overall conclusion and impact on the benefit/risk balance

Benefits

Beneficial effects

Linagliptin 5 mg once daily has been approved for the treatment of adult patients with type 2 diabetes mellitus in combination with several other glucose-lowering medicinal products including metformin and basal insulin.

Jentadueto is a combination of linagliptin 2.5 mg and metformin. Jentadueto twice daily has been approved for the treatment of adult patients with type 2 diabetes mellitus in combination with several other glucose-lowering medicinal products including metformin, but not insulin. Because of the twice daily dosing of metformin, the linagliptin 5 mg is divided in two doses of 2.5 mg.

With the present submission, the MAH is applying for the use of Jentadueto as combination therapy with basal insulin.

Subgroup analyses of two trials investigating linagliptin 5 mg once daily in combination with metformin and insulin were submitted. The triple combination of linagliptin, metformin, and insulin provided clinically meaningful reductions from baseline in HbA1c after 24 weeks compared with the combination of placebo, metformin, and insulin. The adjusted mean treatment differences were -0.68% for patients from the pivotal trial and -0.81% for the elderly patients.
The results of the effects of linagliptin on fasting plasma glucose, the use of rescue medication and the proportions of patients achieving HbA1c targets are in line with the effects on HbA1c. Interestingly, the patients in the placebo+metformin+insulin group needed more insulin than the patients in the linagliptin+metformin+insulin group. The changes in body weight from baseline at 52 weeks were negligible.
There were no important differential treatment effects across the subgroups.

Uncertainty in the knowledge about the beneficial effects

No clinical data investigating the effect of Jentadueto in combination with insulin were submitted. However, bioequivalence of linagliptin 1 dd 5 mg and linagliptin 2 dd 2.5 mg has been demonstrated previously. The effect of insulin on the bioequivalence of linagliptin 1 dd 5 mg and 2 dd 2.5 mg is not known, but kinetic data from the clinical studies demonstrate that the trough levels of linagliptin in combination with insulin are similar compared to historical data of linagliptin without insulin. These data suggest that there is no important pharmacokinetic interaction between linagliptin and insulin. This is also supported by the fact that linagliptin is known to have only minor interactions with other drugs. In addition, effects of insulin on metabolic and transporter enzymes are considered unlikely.

As previously noted, in individuals with diabetes duration less than 1 year, the treatment effect of linagliptin was small. However, this is not a major issue, as most patients that will be treated with a combination of linagliptin and insulin will have longer diabetes duration. Efficacy of linagliptin is acceptable for the investigated subgroups.

Risks

Unfavourable effects

The safety of Jentadueto in combination with basal insulin is likely to be comparable to the safety of linagliptin in combination with metformin and basal insulin.
The frequency of patients who prematurely discontinued treatment was lower for the linagliptin+metformin+insulin group (12.6%) than for the placebo+metformin+insulin group (16.8%). Overall, the proportion of patients with at least one adverse event reported in the on-treatment phase, were comparable between the linagliptin+metformin+insulin group and the placebo+metformin+insulin group (78.0% vs. 80.6%). Proportions of patients with severe adverse events and adverse events leading to treatment discontinuation were similar in both treatment groups (7.3% vs. 8.5% and 4.2% vs. 4.7%, respectively). Serious adverse events were slightly more frequent in the linagliptin+metformin+insulin group than in the placebo+metformin+insulin group (13.8% vs. 12.8%). There were no relevant differences in proportions of patients reported with adverse events leading to premature treatment discontinuation.

There was no evidence that treatment with linagliptin compared with placebo in patients with metformin and insulin background led to an increase in hypoglycaemic events.

The frequency of hepatic adverse events was slightly higher in the linagliptin+metformin+insulin group (2.9%) when compared with the placebo+metformin+insulin group (1.5%). Also slightly more patients in the linagliptin+metformin+insulin group than in the placebo+metformin+insulin group were reported with hypersensitivity adverse events (1.8% vs.1.3%).

There was an increased risk of pancreatitis, which is in line with previous findings with linagliptin (and other DPP-4 inhibitors).

Uncertainty in the knowledge about the unfavourable effects

Compared to the combination of placebo and active comparator on a background of metformin and insulin, cardiovascular events in the group of patients treated with linagliptin were slightly increased (2.6% vs. 1.9%). However, the absolute number of events was low and results are considered inconclusive.

An analysis over time performed for patients from trial 1218.36 only (i.e. the majority [96%] of patients in the pooled safety analysis) showed a greater reduction in mean eCCR over time in the linagliptin+metformin+insulin group than in the placebo+metformin+insulin group, however, this difference disappeared after adjustment for changes in weight. There were differences in deteriorations of microalbuminuria. However, the differences were small and statistical comparisons of the number of patients with deteriorations by means of the Chi-square test did not reveal any indication for a difference between treatment groups (p=0.44 for last value on treatment, p=0.95 for worst value on treatment). In addition, in the overall linagliptin development program, there was no sign of a decrease in renal function. In the dedicated trial conducted in patients with severe chronic renal impairment, there was also no evidence of clinically meaningful changes in renal function for patients treated with linagliptin compared with placebo over 52 weeks.

Benefit-risk balance

Importance of favourable and unfavourable effects

The triple combination of linagliptin, metformin, and basal insulin provided reductions from baseline in HbA1c after 24 weeks compared with the combination of placebo, metformin, and insulin. These reductions may be clinically relevant and associated with reductions in cardiovascular disease. The absolute number of vascular events was low and results are considered inconclusive. Further data from the ongoing cardiovascular outcome study (study 1218.74) is awaited.

The effect of insulin on the bioequivalence of linagliptin 1 dd 5 mg and 2 dd 2.5 mg is not known, but kinetic data from the clinical studies demonstrate that the trough levels of linagliptin in combination with insulin are similar compared to historical data of linagliptin without insulin.

The safety of Jentadueto in combination with insulin appears comparable to the safety of linagliptin in combination with metformin and basal insulin. However, there is an increased frequency of hepatic events with linagliptin/metformin in combination with insulin. This information has been included in the SmPC.

Discussion on the benefit-risk balance

The benefit-risk balance of Jentadueto with basal insulin appears to be similar to that of linagliptin in combination with metformin and basal insulin.

Linagliptin with metformin and insulin is not associated with hypoglycaemia and weight gain. There was an increased risk of hypersensitivity adverse events and pancreatitis, but these risks are in line with previous findings with linagliptin (and other DPP-4 inhibitors) and are listed in the SmPC of Jentadueto. The side effect hepatic events has been included in the SmPC.

The results of the cardiovascular outcome trial are awaited.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change to therapeutic indications - Addition of a new therapeutic indication or modification of an approved one	II

Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC to add a new indication for the use of Jentadueto in combination with insulin in adult patients with type 2 diabetes when insulin and metformin do not provide adequate glycaemic control. The Package Leaflet was updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Conditions and requirements of the marketing authorisation

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.>

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The 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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.