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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Galvus, Jalra and Xiliarx

Procedure No. EMEA/H/C/xxxx/WS/0187

Note

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

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1. Scientific discussion

1.1. Introduction

Vildagliptin is an oral antidiabetic agent which belongs to the dipeptidyl peptidase 4 (DPP-4) inhibitors class. It was first granted a positive opinion by the CHMP for the treatment of type 2 diabetes mellitus (T2DM) in combination with metformin, a thiazolidinedione or a sulphonylurea in July 2007, under the name Galvus. The marketing authorisation was issued by the EU Commission in September 2007. Two additional marketing authorisations were granted in EU for duplicate licenses in November 2008 (Jalra and Xiliarx).

Subsequent to the original application, and as discussed in the EMEA/H/C/771/1048/1051/WS/06/G Type II variation, the MAH (Marketing Authorisation Holder) has accumulated additional safety experience with vildagliptin and has a large pooled clinical database, which now includes information from 38 completed clinical studies of up to more than 2 years duration. It represents more than 11,500 patients treated with vildagliptin (resulting in approximately 9,900 subject years exposure). In addition to assessing general safety as well as selected safety topics of interest, the pooled database was also utilized to conduct an extensive analysis of the safety of vildagliptin in the populations of patients for which CHMP expressed concerns originally. The company has accumulated more experience in CHF patients. In addition the pooled analysis did not reveal any CV (cardiovascular) risk with vildagliptin relative to comparators, including on subgroups of patients at increased CV risk. Furthermore, vildagliptin has been extensively studied in patients with renal impairment. The variation (EMEA/H/C/771/1048/51/WS/149) reached a positive opinion on the 25th Oct 2011, resulting in removal of the restrictions with regards to renal function, recommendations on a reduced posology for patients with moderate to severe (including patients with end-stage renal disease (ESRD)) renal impairment as well as a wording in section 5.1. Since the use of vildagliptin in renal function has been thoroughly discussed within the scope of WS/149, these data is only briefly discussed within the current procedure.

These safety data, together with the efficacy data on vildagliptin as monotherapy, as documented during the original application, have been provided in support of the proposed monotherapy indication in patients who cannot take metformin.

1.2. Non-clinical aspects

Environmental Risk Assessment (ERA)

While this is a type II variation for a new indication, it concerns the same population: patients with type 2 diabetes mellitus. Therefore, there is no need to update the ERA. In addition, in the original MAA, the monotherapy indication was included and the ERA performed at that time covered this indication.

1.3. Clinical Efficacy aspects

The efficacy of vildagliptin as monotherapy has been established in 5 key studies, 2 placebo-controlled and 3 active-controlled (vs. metformin, the sulphonylurea (SU) gliclazide and the thiazolidinedione (TZD) rosiglitazone), which were all previously submitted to CHMP. Key results of these studies are also described in the currently approved SmPC. In addition, 2 active-controlled monotherapy extension

studies (vs. metformin and rosiglitazone) are presented for completeness. Both were part of prior submissions to the CHMP.

Table 1. Summary of monotherapy studies for assessment of efficacy

Study No.	Study objective, population	Randomized patients	Treatment duration	Treatment arms	Comparator
2301	Dose-ranging study – efficacy / safety in drug-naïve T2DM patients (HbA1c 7.5-10.0%)	632	24 weeks	Vilda 50 mg qd Vilda 50 mg bid Vilda 100 mg qd Placebo	Placebo
2384	Dose-ranging study - efficacy / safety in drug-naïve T2DM patients (HbA_{1c} 7.5-10.0%)	354	24 weeks	Vilda 50 mg qd Vilda 50 mg bid Vilda 100 mg qd Placebo	Placebo
2309	Long-term efficacy / safety in drug-naïve T2DM patients (HbA_{1c} 7.5-11.0%)	780	52 weeks	Vilda 50 mg bid Metformin 1000 mg bid	Active
2309E1	*Extension to study 2309*	*463*	*52 weeks*	*Vilda 50 mg bid Metformin 1000 mg bid*	*Active*
2310	Long-term efficacy / safety in drug-naïve T2DM patients (HbA_{1c} 7.5-11.0%)	1092	104 weeks	Vilda 50 mg bid Gliclazide up to 320 mg daily	Active
2327	Efficacy / safety in drug-naïve T2DM patients (HbA_{1c} 7.5-11.0%)	786	24 weeks	Vilda 50 mg bid Rosiglitazone 8 mg qd	Active
2327E1	*Extension to study 2327*	*598*	*80 weeks*	*Vilda 50 mg bid Rosiglitazone 8 mg qd*	*Active*

T2DM = type 2 diabetes; vilda = vildagliptin.

1.3.1. Methods – analysis of data submitted and results

1.3.1.1. Placebo-controlled trials

Table 2 summarizes mean changes in HbA1c from baseline as well as placebo-corrected changes from baseline with vildagliptin 50 mg bid in the two 24-week, placebo-controlled monotherapy studies.

Clinically relevant and statistically significant (vs. placebo) reductions in HbA1c were demonstrated with vildagliptin 50 mg bid in both studies. HbA1c was reduced by -0.79% from a baseline of 8.56% (placebo-subtracted reduction -0.49%) in study 2301 and by -0.72% from a baseline of 8.38% (placebo-subtracted reduction -0.73%) in study 2384. Of note, the placebo response reducing the HbA1c reduction versus placebo seen in study 2301 but not in study 2384 was driven by a cohort of newly diagnosed patients being randomized at or soon after diagnosis.

Vildagliptin 50 mg bid did not cause weight gain in the two studies. Body weight changes from baseline were - 0.3 kg with vildagliptin 50 mg bid and -1.4 kg with placebo in study 2301, and these were -0.0 kg and -1.4 kg, respectively, in study 2384. No hypoglycemic events were reported with vildagliptin 50 mg bid or placebo in either study.

Table 2. Changes in HbA1c (%) with vildagliptin 50 mg bid in placebo-controlled monotherapy studies after 24 weeks of treatment (Primary efficacy populations)

	n	Baseline HbA_{1c} (%) mean (SE)	Change in HbA_{1c} (%) adj. mean (SE)	Difference to placebo mean (SE)	95% CI	p-value
Study 2301	90	8.56 (0.09)	-0.79 (0.13)	-0.49 (0.18)	(-0.84, -0.14)	0.006*
Study 2384	79	8.38 (0.10)	-0.72 (0.14)	-0.73 (0.19)	(-1.11, -0.35)	<0.001*

n is the number of patients with observations at both baseline and endpoint

*indicates statistical significance at 5% level according to the Hochberg step-up procedure

The two studies discussed above were included and assessed within the original MAA. Both studies included additional arms investigating vildagliptin 50 mg qd and 100 mg qd. The conclusion drawn at the time of the MAA was that a clinically relevant effect on HbA1c was achieved with vildagliptin 50 mg bid when given as monotherapy.

1.3.1.2. Active-controlled trials

Large active-controlled monotherapy studies evaluated vildagliptin 50 mg bid compared to metformin and a SU (gliclazide) in studies of 1 to 2 years duration. These studies are summarized below, supporting the proposed positioning of vildagliptin as monotherapy in patients who cannot take metformin.

Comparison to metformin

Study 2309 compared the effects of 52 weeks of treatment with vildagliptin 50 mg bid to metformin up to 1000 mg bid in drug-naïve patients aged 18 to 78 years (HbA1c = 7.5%-11%). A total of 780 patients were randomized to vildagliptin or metformin in a 2:1 ratio.

In the primary analysis population (ITT), baseline HbA1c averaged 8.7% in both treatment groups. Vildagliptin 50 mg bid significantly reduced HbA1c from baseline (-0.96%). This reduction was attained by week 12 and sustained over the 52 week study period. The reduction with metformin (mean dose = 1988 mg/day at final visit) was -1.44%. The associated 95% CI for the between-group difference in mean change was (0.28%, 0.67%) and non-inferiority at a margin of 0.4% was thus not met. Similar results were seen in the PP population, with HbA1c reductions of -1.02% from a baseline of 8.6% with vildagliptin and -1.60% from a baseline of 8.8% with metformin (95% CI for between-group difference 0.36, 0.80). Vildagliptin did not induce weight gain (change from baseline of +0.3 kg; NS), while there was an expected decrease in body weight with metformin (-1.9 kg). The incidence of hypoglycemia was low in both groups: 0.6% of patients receiving vildagliptin and 0.4% of patients receiving metformin experienced one mild hypoglycaemic event each and no serious (grade 2) hypoglycaemic events occurred in either group. The proportion of patients experiencing one or more AEs in the SOC of GI disorders in the metformin group was twice that in patients receiving vildagliptin, due to a 3-4–fold higher percentage of patients in the metformin vs. vildagliptin group reporting diarrhoea, nausea, abdominal pain, dyspepsia, and flatulence.

This study, already assessed within the original MAA, showed that although a clinically relevant effect on HbA1c was observed with vildagliptin 50 mg bid, metformin given at adequate doses showed a significantly better HbA1c lowering effect. Thus the primary target to show non-inferiority in comparison with metformin was not met and only a second line indication, restricted to patients intolerant (or with contraindications) to metformin, could be approvable. The rate of hypoglaecemic

events was comparable between treatments, however, less gastrointestinal adverse events were observed in the vildagliptin treated patients.

Study 2309E1 was a 52 week extension to study 2309. Of the 569 patients completing the core study, 463 patients entered the extension study (305 patients in the vildagliptin treatment arm and 158 in the metformin treatment group). After 104 weeks of treatment, the adjusted mean change from baseline in the primary analysis population (extension ITT) was -0.98% (baseline 8.4%) with vildagliptin 50 mg bid and -1.49% (baseline 8.8%) with metformin 1000 mg bid ($p < 0.001$ vs. vildagliptin). Comparable results were seen in the extension PP population, with HbA1c reductions of -1.14% with vildagliptin (baseline 8.4%) and -1.54% with metformin (baseline 8.8%, $p=0.002$ vs. vildagliptin). These reductions were very similar to those reported after the 1 year core phase of the study, i.e., both vildagliptin and metformin monotherapy sustained a clinically meaningful decrease in HbA1c throughout 2 years of treatment. Body weight, hypoglycemia and GI tolerability were also comparable to the 1 year data.

Comparison to SU

Study 2310 was a multicenter, randomized, double-blind, active-controlled study to compare the efficacy and safety of long-term treatment (104 weeks) with vildagliptin 50 mg bid to gliclazide up to 320 mg daily in drug-naïve patients with T2DM (HbA1c 7.5%-11%). Eligible patients (N=1092) were randomized to vildagliptin or gliclazide in a ratio of 1:1.

Both treatment groups achieved clinically relevant reductions in HbA1c from baseline to Week 104 (endpoint), i.e. -0.47% in the vildagliptin 50 mg bid group and -0.61% in the gliclazide group from a mean baseline HbA1c of 8.5% and 8.7%, respectively, in the primary (PP) analysis population. The associated 95% CI for the between-group difference in mean change was (-0.06%, 0.33%). The study narrowly failed to show non-inferiority at a margin of 0.3% in the analysis at 104 weeks. Vildagliptin did not induce relevant weight gain and vildagliptin-treated patients reported less hypoglycaemic events. There was a distinct increase in body weight in the comparator group (mean +1.6 kg increase from baseline, compared to +0.8 kg in the vildagliptin group). The number of patients who experienced a hypoglycaemic event was low across the study, but was higher in the gliclazide group (1.7% vs. 0.7% in the vildagliptin group).

This study was assessed within procedure EMEA/H/C/771/II/04. It was concluded that it failed to demonstrate non-inferiority of vildagliptin compared to gliclazide. The absolute reduction of HbA1c with vildagliptin was somewhat lower compared to the comparator. Thus, there are indications that vildagliptin may be somewhat less effective compared to SU. A description of this study was included in the SPC, section 5.1. Concerning safety, vildagliptin had a hypoglycemia profile superior to that of SU.

Additional data

While no longer a marketed drug in the EU, a 24-week study (Study 2327) compared vildagliptin 50 mg bid to the TZD rosiglitazone (8 mg qd). In the primary analysis population (primary ITT) mean HbA1c reductions were -1.13% with vildagliptin and -1.32% with rosiglitazone from baselines of 8.7%, and statistical non-inferiority was established at a non-inferiority margin of 0.4%. The HbA1c reductions in the PP population (-1.20% vs. -1.48%) were essentially consistent with those seen in the primary ITT population, however, non-inferiority was not achieved. Patients receiving vildagliptin 50 mg bid experienced no weight gain (-0.3 kg) while those receiving rosiglitazone experienced a mean increase in weight of + 1.6 kg.

1.3.2. Discussion on Efficacy

The studies supporting the monotherapy indication were already submitted in initial MAA and subsequent type II variations.

Two placebo-controlled studies were included and assessed within the original MAA. Both studies included additional arms investigating vildagliptin 50 mg qd and 100 mg qd. The conclusion drawn at the time of the MAA was that a clinically relevant effect on HbA1c was achieved with vildagliptin 50 mg bid when given as monotherapy.

In a study designed to show non-inferiority for vildagliptin vs metformin (already assessed within the original MAA) it was shown that, although a clinically relevant effect on HbA1c was observed with vildagliptin 50 mg bid, metformin given at adequate doses showed a significantly better HbA1c lowering effect. Thus the primary target to show non-inferiority in comparison with metformin was not met and only a second line indication, restricted to patients intolerant (or with contraindications) to metformin, could be approvable. In the long-term extension of this study efficacy was maintained over the two-year study period in both study groups. Hypoglycaemic events were comparable between treatments, however, less gastrointestinal events were observed in the vildagliptin treated group.

A study designed to show non-inferiority for vildagliptin vs a SU (gliclazide) in drug-naïve patients was assessed within procedure EMEA/H/C/771/II/04. It was concluded that it failed to demonstrate non-inferiority of vildagliptin compared to gliclazide. The absolute reduction of HbA1c with vildagliptin was somewhat lower compared to the comparator. However, the weight gain was less pronounced with vildagliptin and there was a trend towards less hypoglycaemia compared to gliclazide treatment. A description of this study was included in the SPC, section 5.1.

In a comparative study vs rosiglitazone, clinically relevant effects on HbA1c were observed and vildagliptin was essentially weight neutral. This study failed to show non-inferiority for vildagliptin vs rosiglitazone in the PP-population.

Further to these studies, two new studies investigating the use of vildagliptin in patients with moderate to severe renal impairment have been submitted and discussed in the recently finalised Type 2 variation (EMEA/H/C/771/WS/149). This variation reached a positive opinion on the 25th Oct 2011, resulting in deletion of the restrictions with regards to renal function, recommendations on a reduced posology for patients with moderate to severe (including patients with ESRD) renal impairment as well as a wording in section 5.1.

The efficacy of vildagliptin to lower HbA1c when used as monotherapy has been adequately shown with consistent findings of across studies. In all comparative studies the absolute reduction of HbA1c with vildagliptin was lower compared to the comparators, thus only a monotherapy indication restricted to the use in patients intolerant or with contraindications to metformin (including renal impairment) as proposed by the MAH is acceptable.

1.4. Clinical Safety aspects

Since the original submission the clinical study dataset has been expanded, now comprising information from 38 completed clinical studies of up to more than 2 years duration. It represents more than 11,500 patients treated with vildagliptin (resulting in approximately 9,900 subject years exposure) as discussed in the recent Type II variation applications.

No new safety issues have been identified during PSUR assessments.

A detailed overview of the most current analyses of the safety and tolerability of vildagliptin is presented within the submission of the EMEA/H/C/771/WS/06/G Type 2 variation.

A detailed discussion of these data is included in the AR for procedure EMEA/H/C/771/WS/06/G. It was concluded that no new safety signals have been identified.

Based on the CHMP assessment of the original application, following safety aspects are particular relevance for the proposed 2nd line monotherapy indication:

- A review of the safety of vildagliptin in patients with CHF based on the enlarged experience with the product in this patient population as well as a summary of the CCV safety of vildagliptin in the overall population including patients at increased CV risk, to document absence of a CV safety signal in the overall population and in particular a high CV risk population.

  The safety analyses in patients with CHF and the CV safety analyses in the overall population are based on the pooled dataset described above.

- A review of the safety of vildagliptin in patients with moderate or severe renal impairment.

The safety analyses in patients with moderate or severe renal impairment are based on two recently completed, stand-alone studies, which are not part of the pooled dataset (see EMEA/H/C/771/1048/1051/WS/149). As a result of the variation the restrictions previously given for the treatment of patients with impaired renal function have been removed. A reduced posology (50 mg qd) has been amended for patients with moderate to severe renal (including patients with end-stage renal disease (ESRD)) impairment.

1.4.1. Safety in patients with CHF

To provide an assessment of the safety of vildagliptin when administered to diabetic patients with CHF, an evaluation of the overall AE profile of vildagliptin as well as of AEs related to the CV system in this population are presented.

Patients were considered to have CHF if one or more of the MedDRA (Medical Dictionary for Regulatory Activities) Preferred Terms included in the 'Level 1 Standardized MedDRA Query (SMQ): Cardiac failure, narrow search' were present in the medical history at baseline. Of note, patients with CHF NYHA class III and IV were generally excluded from the clinical studies.

These analyses were previously presented in the EMEA/H/C/771/WS/06/G Type II variation application and are also outlined within current submission. For ease of reference, a summary of the data is provided below.

Exposure

In the original application, a total of 72 patients with a history of CHF were identified in the integrated monotherapy and add-on dataset presented, including 43 vildagliptin-treated patients and 29 patients in the all comparator group (including 14 patients treated with placebo). Additional data from 19 patients with a history of CHF treated with vildagliptin in Study 2308 were also presented.

In the current expanded dataset (all studies [excluding open-label] safety population), a total of 184 patients with a history of CHF at study entry have been identified, including 131 who received vildagliptin treatment and 53 who received comparator treatment. The majority of vildagliptin patients (70%) were treated with the 50 mg bid dose (Table 3).

Table 3. Of note, the mean duration of exposure was very similar between the vildagliptin 50 mg bid (52.3 weeks) and all comparators (51.5 weeks) groups, allowing for direct comparisons between these two tables

	Vilda 50 mg qd	Vilda 50 mg bid	Vilda 100 mg qd	Total Vilda	Total Placebo	Total Comparators

	Vilda 50 mg qd	Vilda 50 mg bid	Vilda 100 mg qd	Total Vilda	Total Placebo	Total Comparators
Patient (N)	20	91	20	131	18	53
Mean duration (wks)	31.1	52.3	22.9	44.6	32.1	51.5
Exposure (SYE)	11.9	91.2	8.8	111.9	11.1	52.3

Total comparators = placebo plus active comparators

The number of patients with CHF is still considered to be limited.

Demographic and background characteristics

Compared to the overall population, vildagliptin-treated patients with a history of CHF were as expected older (mean age = 64 vs. <56 years), had a somewhat higher BMI (32.9 vs. 31.4 kg/m2) and a higher percentage of patients had mild renal impairment (nearly 1/2 vs. approximately 1/3). On the other hand, glycaemic control (mean HbA1c = 8.0% vs. 8.2%) and disease duration (mean = 4.9 vs. 4.2 years) were similar in the two populations. Overall similar baseline characteristics were observed in the CHF patient group exposed to all comparators.

Adverse Events

As shown in Table 4, the overall percentage of CHF patients with any AE was similar for vildagliptin 50 mg bid (60.4%) and all vildagliptin (61.8%) vs. all comparators (62.3%) and lower than that observed with placebo (77.8%). There was no dose-response relationship.

The distribution of AEs by primary SOC was also similar across groups. The four SOCs with the highest incidences of AEs across treatment groups were 'Infections and Infestations' (28.6% with vildagliptin 50 mg bid, 29.0% with all vildagliptin and 32.1% with all comparators), 'Nervous System Disorders' (23.1% with vildagliptin 50 mg bid, 24.4% with all vildagliptin and 20.8% with all comparators), 'Gastrointestinal Disorders' (17.6% with vildagliptin 50 mg bid, 17.6% with all vildagliptin and 13.2% with all comparators) and 'Musculoskeletal and Connective Tissue Disorders' (14.3% with vildagliptin 50 mg bid, 13.0% with all vildagliptin and 24.5% with all comparators). No meaningful imbalances were observed in the overall reporting rates of AEs under the hepatobiliary, skin and vascular SOCs between vildagliptin 50 mg bid and all vildagliptin vs. all comparators. The most notable differences were observed in the 'Investigations' SOC with incidences of 1.1% for vildagliptin 50 mg bid, 1.5% for all vildagliptin and 13.2% for all comparators, mainly driven by differences in the Preferred Terms of 'blood glucose decreased' and 'weight increased'.

Table 4. Number (%) of patients with AEs by primary SOC in patients with a medical history of CHF (all studies [excluding open-label] safety population)

Primary SOC n (%)	Vilda 50 mg qd N=20	Vilda 50 mg bid N=91	Vilda 100 mg qd N=20	Total Vilda N=131	Total Placebo N=18	Total Comparators N=53
Any primary SOC	**15 (75.0)**	**55 (60.4)**	**11 (55.0)**	**81 (61.8)**	**14 (77.8)**	**33 (62.3)**
Blood and lymphatic system disorders	1 (5.0)	3 (3.3)	2 (10.0)	6 (4.6)	0 (0.0)	2 (3.8)
Cardiac disorders	2 (10.0)	12 (13.2)	0 (0.0)	14 (10.7)	0.(0.0)	8 (15.1)
Congenital, familial and genetic disorders	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	1 (5.0)	3 (3.3)	0 (0.0)	4 (3.1)	0 (0.0)	1 (1.9)
Eye disorders	2 (10.0)	3 (3.3)	1 (5.0)	6 (4.6)	0 (0.0)	4 (7.5)
Gastrointestinal disorders	5 (25.0)	16 (17.6)	2 (10.0)	23 (17.6)	2 (11.1)	7 (13.2)
General disorders & administration site conditions	5 (25.0)	11 (12.1)	3 (15.0)	19 (14.5)	2 (11.1)	7 (13.2)

Primary SOC n (%)	Vilda 50 mg qd N=20	Vilda 50 mg bid N=91	Vilda 100 mg qd N=20	Total Vilda N=131	Total Placebo N=18	Total Comparators N=53
Hepatobiliary disorders	0 (0.0)	2 (2.2)	0 (0.0)	2 (1.5)	1 (5.6)	2 (3.8)
Immune system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (1.9)
Infections and infestations	8 (40.0)	26 (28.6)	4 (20.0)	38 (29.0)	8 (44.4)	17 (32.1)
Injury, poisoning and procedural complications	2 (10.0)	9 (9.9)	1 (5.0)	12 (9.2)	3 (16.7)	7 (13.2)
Investigations	1 (5.0)	1 (1.1)	0 (0.0)	2 (1.5)	1 (5.6)	7 (13.2)
Metabolism and nutrition disorders	0 (0.0)	7 (7.7)	0 (0.0)	7 (5.3)	3 (16.7)	4 (7.5)
Musculoskeletal and connective tissue disorders	2 (10.0)	13 (14.3)	2 (10.0)	17 (13.0)	5 (27.8)	13 (24.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	3 (3.3)	0 (0.0)	3 (2.3)	1 (5.6)	3 (5.7)
Nervous system disorders	8 (40.0)	21 (23.1)	3 (15.0)	32 (24.4)	4 (22.2)	11 (20.8)
Psychiatric disorders	2 (10.0)	4 (4.4)	2 (10.0)	8 (6.1)	2 (11.1)	5 (9.4)
Renal and urinary disorders	2 (10.0)	7 (7.7)	0 (0.0)	9 (6.9)	1 (5.6)	5 (9.4)
Reproductive system and breast disorders	0 (0.0)	4 (4.4)	0 (0.0)	4 (3.1)	1 (5.6)	4 (7.5)
Respiratory, thoracic and mediastinal disorders	1 (5.0)	10 (11.0)	0 (0.0)	11 (8.4)	2 (11.1)	5 (9.4)
Skin and subcutaneous tissue disorders	2 (10.0)	13 (14.3)	1 (5.0)	16 (12.2)	4 (22.2)	7 (13.2)
Surgical and medical procedures	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (1.9)
Vascular disorders	1 (5.0)	15 (16.5)	1 (5.0)	17 (13.0)	0 (0.0)	6 (11.3)

Primary system organ classes are presented alphabetically. Preferred terms are sorted within primary system organ class alphabetically. A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. A patient with multiple AEs within a system organ class is counted only once in the total row.
Total comparators = placebo plus active comparators.

CHMP is of opinion that due to the small numbers, these data has to be interpreted with caution, however, no gross imbalances was observed between vildagliptin treated patients and patients treated with active comparators. Notably the rate of cardiac adverse events was somewhat lower in the vildagliptin treated groups compared to active comparator but higher than placebo (only 18 patients).

Cardiac (arrhythmic, heart failure-related and ischemic) adverse events

To further evaluate the effect of vildagliptin on AEs related to the CV system in patients with a medical history of CHF, the incidences of selected cardiac (i.e. arrhythmic, heart-failure related, ischemic) AEs are presented in Table 1.

The analysis did not indicate an increased incidence of cardiac (i.e. arrhythmic, heart-failure related, ischemic) AEs with vildagliptin relative to all comparators.

The incidence of any such AE was slightly lower with vildagliptin 50 mg bid (9.9%) and all vildagliptin (8.4%) than that observed for all comparators (13.2%). This was also true for any arrhythmic AEs (4.4% with vildagliptin 50 mg bid, 3.1% with all vildagliptin and 9.4% with all comparators) and any heart-failure related AEs (6.6% with vildagliptin 50 mg bid, 6.1% with all vildagliptin and 7.5% with all comparators). The incidence of ischemic events was similar between vildagliptin 50 mg bid (2.2%), all vildagliptin (1.5%) and all comparators (1.9%).

The analysis of AEs by SOC as presented in Table 5-2, also revealed a similar or lower overall incidence of AEs in the 'Cardiac Disorders' SOC with vildagliptin 50 mg bid (13.2%) and all vildagliptin (10.7%) relative to all comparators (15.1%).

Table 1. Number (%) of patients with selected cardiac (arrhythmic, heart failure-related and ischemic) AEs by preferred term in patients with a medical history of CHF (all studies [excl open-label] safety population)

Event category Preferred term n (%)	Vilda 50 mg qd N=20	Vilda 50 mg bid N=91	Vilda 100 mg qd N=20	Total Vilda N=131	Total Placebo N=18	Total Comparators N=53
Any event category	**2 (10.0)**	**9 (9.9)**	**0 (0.0)**	**11 (8.4)**	**0 (0.0)**	**7 (13.2)**
Arrhythmic events						
Any arrhythmic AE	**0 (0.0)**	**4 (4.4)**	**0 (0.0)**	**4 (3.1)**	**0 (0.0)**	**5 (9.4)**
Atrial fibrillation	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.8)	0 (0.0)	1 (1.9)
Atrial flutter	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Atrioventricular block	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Atrioventricular block first degree	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.8)	0 (0.0)	1 (1.9)
Atrioventricular block second degree	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Bundle branch block left	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Bundle branch block right	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Extrasystoles	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Sinus tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.8)
Supraventricular extrasystoles	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Heart-failure-related events						
Any heart-failure-related AE	**2 (10.0)**	**6 (6.6)**	**0 (0.0)**	**8 (6.1)**	**0 (0.0)**	**4 (7.5)**
Cardiac failure	0 (0.0)	2 (2.2)	0 (0.0)	2 (1.5)	0 (0.0)	4 (7.5)
Cardiac failure acute	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Cardiac failure congestive	1 (5.0)	2 (2.2)	0 (0.0)	3 (2.3)	0 (0.0)	1 (1.9)
Pulmonary oedema	1 (5.0)	1 (1.1)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)
Right ventricular failure	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Ischemic events						
Any ischemic AE	**0 (0.0)**	**2 (2.2)**	**0 (0.0)**	**2 (1.5)**	**0 (0.0)**	**1 (1.9)**
Acute myocardial infarction	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	2 (2.2)	0 (0.0)	2 (1.5)	0 (0.0)	1 (1.9)

Event categories are presented alphabetically; Preferred terms are sorted within event category alphabetically. A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. A patient with multiple AEs within an event category is counted only once in the total row. Total Total comparators = placebo plus active comparators.

CHMP is of opinion that the detailed analysis of cardiac events did not reveal any safety concerns.

Conclusion

A total of 131 vildagliptin-treated patients with a history of CHF at study entry were identified in the current dataset (all studies [excluding open-label] safety population). There was no evidence of an adverse safety signal in these patients. In particular, analysis of data in patients with documented CHF did not indicate an increased incidence of overall AEs or cardiac (i.e. arrhythmic, heart failure-related or ischemic) AEs with vildagliptin relative to all comparators.

The cardiac safety of vildagliptin in patients with CHF is further characterized through a prospective randomized safety study (Study 23118, -indicated as an additional pharmacovigilance activity in the pharmacovigilance plan of the RMP), which is currently ongoing. However, the Company believes that

the pooled data presented allow for meaningful conclusions before the results of the ongoing study are available and support the proposed monotherapy indication.

As discussed in the AR concerning EMEA/H/C/771/WS/06/G, the analysis of data in patients with documented CHF did not indicate an increased incidence of overall AEs or cardiac (i.e. arrhythmic, heart failure-related or ischaemic) AEs with vildagliptin relative to all comparators. However, the number of patients was rather low, and patients with CHF III-IV were generally excluded from the studies. The cardiac safety of vildagliptin in patients with CHF will be further characterized through a prospective randomized safety study which is indicated as an additional pharmacovigilance activity in the pharmacovigilance plan of the RMP.

The additional data is, however, considered sufficient in mitigating the concerns raised during the original MAA and the limitations of the data does not preclude the approval of the monotherapy indication. It is proposed that the current warnings in section 4.4 of the SmPC regarding the lack of data in patients with CHF are changed to only include patients with NYHA III-IV. The CHMP agreed and the SmPC has been updated accordingly.

1.4.2. Cardiovascular and cerebrovascular safety in the overall population

In order to further document the CCV safety of vildagliptin, its CCV safety in the overall population including patients at increased CV risk was analyzed and the analyses are also in line with the CHMP revised draft "Note for Guidance of Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus", addressing the issue of CV assessments required for new or recently approved antidiabetic drugs. These analyses were presented in detail in the EMEA/H/C/771/WS/06/G Type II variation application and are also outlined in the current addendum. This supportive information is therefore only briefly summarized hereafter for ease of reference.

The population studied for these analyses was representative of a T2DM population with multiple CV risk factors and with ~ 1/6 of patients (N=1438) having a high CV risk status (defined as a previous history of events in the SMQs of cardiac failure, embolic/thrombotic events arterial, ischemic heart disease and/or ischemic cerebrovascular conditions).

Vildagliptin was not associated with an increased risk of confirmed CCV events as adjudicated by a pre-planned independent Adjudication Committee [i.e. acute coronary syndrome, transient ischemic attack (imaging evidence of infarction), stroke (ischemic and hemorrhagic), and CCV death], SMQ MACE events or Custom MACE events relative to all comparators. The risk ratios (all vildagliptin vs. all comparators) were 0.84 (adjudicated CCV events), 0.82 (SMQ MACE) and 0.89 (Custom MACE), respectively. Furthermore, these risk ratios for the 3 endpoints analyzed met the FDA guidance criterion of an upper limit of the 95% CI less than 1.3.

Subgroup analyses by age, gender, CV risk status and duration of diabetes were performed to address applicability of results in higher CV risk populations. Overall there was no increased risk of adjudicated CCV events or MACE events with vildagliptin in these subgroups consistent with the overall result.

The analysis above is further supported by a separate analysis of arrhythmic, heart failure-related or cardiac ischemic events, which demonstrated that vildagliptin at the approved doses was not associated with an increased risk relative to all comparators.

Conclusion

The following assessment was made of the CV data in EMEA/H/C/771/WS/06/G: *The analyses of adjudicated CCV events (ACS, TIA [with imaging evidence of infarction], stroke and CCV death) and MACE (SMQ or Custom) events demonstrated that vildagliptin was not associated with an increased*

risk of CCV events relative to all comparators. The incidence of SMQ MACE events was similar between the vildagliptin 50 mg bid group (2.1%) and the all comparators group (2.3%). The risk ratios (all vildagliptin vs. all comparators) for the three endpoints analyzed (adjudicated CCV events, SMQ MACE and Custom MACE) met the FDA guidance criterion of an upper limit of the 95% CI less than 1.3. This may seem reassuring, however, it should be remembered that the mean duration of exposure is less than 50 weeks and only 16-18% of the population was defined as having high CV risk status. Thus, it may be questioned whether this scenario reflects the clinical situation and population.

Taken together, the data indicate that vildagliptin is not associated with an increased CV risk in the overall population or in subgroups of patients at increased CV risk.

1.4.3. Safety in patients with moderate or severe renal impairment

An additional patient population of particular relevance in the context of the proposed monotherapy indication are patients with moderate or severe renal impairment.

The safety and tolerability of vildagliptin in these patients has been established in two large, stand-alone, 24-week studies (23137 and 23138). The results of these studies were recently submitted to CHMP as part of an application to remove the label restriction for vildagliptin in patients with moderate or severe renal impairment (EMEA/H/C/771/WS/149), which reached a positive opinion in October 2011.

The safety and tolerability of vildagliptin has been studied in 371 patients with moderate (N=165) or severe (N=206) renal impairment. In line with the PK data, a dose of 50 mg qd was chosen for these studies.

The main study to establish the safety and tolerability of vildagliptin in patients with moderate and severe renal impairment is study 23137, which compared vildagliptin to placebo. Additional supportive information comes from study 23138, which evaluated vildagliptin in comparison to another DPP-4 inhibitor, sitagliptin, in patients with severe renal impairment.

Taken together, the available clinical data from studies 23137 and 23138 demonstrate that vildagliptin 50 mg qd is well tolerated in patients with moderate or severe renal impairment, with no new safety signals or unforeseen risks identified.

The safety data from studies 23137 and 23138 have been thoroughly discussed in the procedure EMEA/H/C/771/WS/149 for which an opinion was adopted in October 2011. It was concluded that the safety data provided in patients with moderate and severe renal impairment is considered sufficient to recommend treatment in these populations.

1.4.4. Laboratory findings

Clinical chemistry, hematology, urinalysis, special tests

No new information has become available, which would affect vildagliptin use in monotherapy indication.

1.4.5. Safety in special populations

The special patient populations of particular relevance in the context of the proposed monotherapy indication have been discussed above.

The safety of vildagliptin in elderly (≥65 years) was assessed in a type II variation (EMEA/H/C/771/807/1048/051/1050/1049/WS/70). It was concluded that "the submitted analyses

support a similar efficacy in elderly patients compared to the younger population with respect to reduction of HbA1c and FPG. The treatment was largely weight neutral and the incidence of hypoglycaemia was low. No other safety issues compared to comparators or the younger population were identified." Thus, it was agreed that the wording in section 4.2 recommending caution in elderly patients aged 75 years and older could be removed.

1.4.6. Prematurely discontinued and unfinished studies

No studies were prematurely discontinued.

Main ongoing studies at the time of this application include a study in T2DM patients with CHF (Study 23118), as discussed above, and two other studies (Study 23152 and Study 23135). No unexpected safety events were reported in any of these trials.

1.4.7. Post marketing experience

Long-term use

Data from long-term studies with vildagliptin did not identify any particular safety signals or unforeseen risks for long-term use, as discussed in the previous Type 2 variation applications and also summarized in the current SCS-Addendum.

Post-marketing experience

Vildagliptin is currently approved in more than 80 countries worldwide and the fixed dose combination of vildagliptin/metformin in more than 75 countries worldwide.

Based on the sales data there is a significant post-marketing patient exposure to vildagliptin and vildagliptin/ metformin

The safety of the product is continuously monitored and reported to Health Authorities regularly via PSURs. PSUR data continue to support the current assessment of the benefit/risk of vildagliptin.

Following a request by the CHMP (EMA/549257/2010), the MAH has recently conducted a thorough evaluation of all reports related to liver dysfunction received from marketed use of vildagliptin (including Galvus and Eucreas) since the original placing on the market. The review was assessed in a type II variation (EMEA/H/C/771/807/1048/1051/1050/1049/WS/125). Seven cases consistent with a drug-related liver event were identified. Based on these cases, the safety information referring to the post-marketing experience in section 4.8 has been updated to reflect the safety concern of drug-related liver disease.

1.4.8. MAH's safety conclusions

Subsequent to the original application, the company has accumulated significant additional safety experience in patients with CHF as well as patients with moderate or severe renal impairment as outlined below.

The additional clinical data, including from long-term clinical studies, demonstrated in a considerably enlarged dataset that vildagliptin is not associated with an increased risk for AEs, including cardiovascular AEs, relative to comparators in patients with T2DM and CHF. Novartis acknowledges that the number of patients with more advanced CHF (NYHA class 3 and 4) recruited in clinical trial remains limited, which the product label reflects (SmPC Section 4.4), and is confirming the safety of

vildagliptin in patients with CHF in a dedicated clinical study, which is currently ongoing (Study 23118 indicated as an additional pharmacovigilance activity in the pharmacovigilance plan of the RMP). However, the MAH believes that the available data in patients with CHF are adequate to support the proposed monotherapy indication for the following reasons:

- The current analyses in a meaningful number of T2DM patients with CHF do not reveal any safety signals for vildagliptin treatment as compared to comparators in this population.
- The nature and incidences of cardiovascular AEs in T2DM patients with CHF were similar between the vildagliptin and comparators treatment groups.
- In the overall population, vildagliptin is not associated with an increased risk of confirmed CCV events (as adjudicated by a pre-planned independent Adjudication Committee) or SMQ / Custom MACE events relative to all comparators, even within sub-populations of patients with high CV risk. Of note, this includes a subpopulation of more than 1,400 vildagliptin-treated patients with a previous history of events in the SMQs of cardiac failure, embolic/thrombotic events arterial, ischemic heart disease and/or ischemic cerebrovascular conditions.

Furthermore, vildagliptin has been extensively studied in patients with renal impairment. Vildagliptin was shown to be efficacious and overall well tolerated in patients with moderate or severe renal impairment, with a positive benefit/risk evaluation in these patient populations at a proposed dose of 50 mg qd. The observed efficacy with vildagliptin 50 mg qd in patients with moderate or severe renal impairment was of similar magnitude to that seen with vildagliptin 50 mg bid in the overall population with a similar baseline HbA1c range (EMEA/H/C/771/1048/1051/WS/149). The overall safety profile of vildagliptin in patients with moderate or severe renal impairment was comparable to placebo, with no new safety signals or unforeseen risks identified. The data from the two large clinical trials, in which 371 patients with moderate or severe renal impairment were treated with vildagliptin, have recently been submitted to CHMP (EMEA/H/C/771/1048/1051/WS/149 Type 2 variation application), and positive opinion was reached in Oct 2011, removing restrictions regarding the use in patients with renal impairment.

In addition, the proposed use of vildagliptin as 2nd line monotherapy in patients who cannot take metformin is further supported as follows.

- A restriction for vildagliptin's use in elderly patients ≥ 75 years was removed in December 2010 (CHMP opinion), based on increased experience and a favourable benefit/risk evaluation in this patient population.
- Monotherapy treatment with vildagliptin 50 mg bid in drug-naive patients with T2DM resulted in statistically significant, clinically relevant and sustained HbA1c reductions across studies in a broad type 2 diabetic population. Although vildagliptin was less efficacious than metformin in a 1 year study, it demonstrated a significantly better GI tolerability profile. This underlies the company's proposal to register vildagliptin as monotherapy in patients who cannot take metformin due to intolerance.

The robust efficacy and safety/tolerability data presented in this application support that vildagliptin may constitute a suitable alternative to SU or TZD monotherapy. In this context it is noteworthy that the efficacy of vildagliptin 50 mg bid as monotherapy was shown to be of similar magnitude to the SU gliclazide (although non-inferiority was narrowly missed) in a study of 2 years duration, with clinically relevant advantages, including a low risk of hypoglycemia and no weight gain. Vildagliptin has also been demonstrated to provide comparable efficacy to rosiglitazone in a 24-week study (non-inferiority established in the primary analysis population) without the weight gain of the TZD.

Furthermore, in addition to the established safety and tolerability in the special patient populations discussed earlier, the (long-term) safety of vildagliptin alone and in combination with other antidiabetic drugs has been demonstrated in a large pool of patients, including data from 38 clinical trials of up to more than 2 years in duration, which further support that vildagliptin can be used safely in a broad range of T2DM patients. This includes a comprehensive assessment of hepatic safety, which has been performed based on data from the extensive clinical trial database coupled with a review of the increasing post-marketing experience. These data, as discussed in detail in previous submissions, support use of vildagliptin at a 50 mg bid regimen in clinical practice.

Taken together, relevant new information is available, which support a positive benefit/risk for the use of vildagliptin as monotherapy in T2DM patients who cannot take metformin due to intolerance or contraindications. This includes patients with CHF or renal impairment, including elderly patients.

In addition, the company proposes that the risk management activities outlined in the RMP are appropriate to ensure a safe use of the product in the new proposed indication.

1.4.9. Discussion

The studies supporting the monotherapy indication were already submitted in initial MAA and subsequent type II variations.

At the time of the original MAA, the CHMP raised concerns regarding the use of vildagliptin as monotherapy in patients with CHF since the number of patients included in the studies was low. Further to this, due to lack of data in patients with renal impairment, the use of vildagliptin in patients with contraindications to metformin (mainly renal impairment) was not recommendable by the CHMP.

As discussed in the AR concerning EMEA/H/C/771/WS/06/G, the analysis of data in patients with documented CHF did not indicate an increased incidence of overall AEs or cardiac (i.e. arrhythmic, heart failure-related or ischaemic) AEs with vildagliptin relative to all comparators. The number of patients was rather low, and patients with CHF NYHA III-IV were generally excluded from the studies. The detailed analysis of cardiac events, however, did not reveal any safety concerns. The cardiac safety of vildagliptin in patients with CHF will be further characterized through a prospective randomized safety study (LAF237A23118).

These additional data are considered sufficient in mitigating the concerns raised during the original MAA and the limitations of the available data does not preclude the approval of the monotherapy indication. It is proposed that the current warnings in section 4.4 of the SPC regarding the lack of data in patients with CHF are changed to only include patients with NYHA III-IV.

An analysis of CV data was assessed in EMEA/H/C/771/WS/06/G. It was concluded that the analyses of adjudicated CCV events and MACE events demonstrated that vildagliptin was not associated with an increased risk of CCV events relative to all comparators. It should, however, be remembered that the mean duration of exposure is less than 50 weeks and only 16-18% of the population was defined as having high CV risk status. Although these data may not fully reflect the clinical situation and target population, there are no signals of a negative effect of vildagliptin on CV safety.

Further to this, the safety of vildagliptin in elderly (≥65 years) was assessed in a type II variation (EMEA/H/C/771/807/1048/051/1050/1049/WS/70). It was concluded that the submitted analyses support a similar efficacy in elderly patients compared to the younger population with respect to reduction of HbA1c and FPG with a similar safety profile in elderly. As a result of this variation the wording in section 4.2 recommending caution in elderly patients aged 75 years and older could be removed.

Following a request by the CHMP (EMA/549257/2010), the MAH has recently conducted a thorough evaluation of all reports related to liver dysfunction received from marketed use of vildagliptin (including Galvus and Eucreas) since the original placing on the market. The review was assessed in a type II variation (EMEA/H/C/771/807/1048/1051/1050/1049/WS/125). Seven cases consistent with a drug-related liver event were identified. Based on these cases, the safety information referring to the post-marketing experience in section 4.8 has been updated to reflect the safety concern of drug-related liver disease.

Additional safety data from two studies in a total of 371 patients with moderate and severe renal impairment has recently been assessed in variation EMEA/H/C/771/WS/149. It was concluded that the safety profile did not appear different in this population compared to the overall population when a reduced posology of 50 mg qd was applied. As a result of this variation the restrictions previously given for the treatment of patients with impaired renal function have been removed.

The additional safety data obtained after the initial approval of vildagliptin is considered sufficient in addressing the concerns raised regarding the use of vildagliptin in patients with CHF and renal impairment. It is proposed that the warnings regarding patients with CHF included in section 4.4 of the SPC is changed to only include patients with NYHA III-IV due to lack of data in this patient group.

1.5. Risk management plan

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

In addition, the CHMP considered that the applicant should take the following minor points into consideration when an update of the Risk management Plan is submitted:

The MAH should consider removing *patients with moderate or severe renal impairment*, *patients with compromised cardiac function (NYHA functional class I-II)* and *elderly patients* from the "missing information" section. Furthermore, *drug-induced liver injury* should be escalated from an "important potential risk" to an "important identified risk" and RMP should be updated with additional data regarding the safety of DDP-4 inhibitors in patients with cardiovascular disease.

1.6. Changes to the Product Information

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

4.1 Therapeutic indications

Vildagliptin is indicated in the treatment of type 2 diabetes mellitus:

As monotherapy

- **in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.**

[…]

4.2 Posology and method of administration

Adults
When used **as monotherapy** or in dual combination with metformin or a thiazolidinedione, the recommended daily dose of vildagliptin is 100 mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening.

[…]

During the procedure, the CHMP requested further amendments to the PI as discussed in detail in section 2.4.1 Safety in patients with CHF. The following additional amendments to the PI have been accepted by the CHMP:

4.4 Special warnings and precautions for use

[…]

Cardiac failure
Experience with vildagliptin therapy in patients with congestive heart failure of New York Heart Association (NYHA) functional class I-II is limited and therefore vildagliptin should be used cautiously in these patients. There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class III-IV and therefore use is not recommended in these patients.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, which were accepted by the CHMP.

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

The present variation aims at providing overview of safety and efficacy data in support of a monotherapy indication in patients for whom metformin is inappropriate due to intolerance (i.e. including patients with GI side-effects) or contraindications (i.e. including patients with CHF or renal impairment). No new data have been submitted, but all data have been previously assessed either in the original MAA or in subsequent procedures.

The efficacy of vildagliptin to lower HbA1c when used as monotherapy has been adequately shown in two placebo-controlled studies and three studies with active comparator. The results were consistent across studies showing a placebo-corrected 0.49-0.73 % lowering of HbA1c over 24 weeks. In the active comparator studies the HbA1c decreased with 0.47 to 1.13 % (study durations between 24 and 104 weeks). In all comparative studies the absolute reduction of HbA1c with vildagliptin was lower compared to the comparators. In the study where vildagliptin was compared to metformin, significantly better results were observed with metformin, thus only a monotherapy indication restricted to the use in patients intolerant or with contraindications to metformin (including renal impairment) could be acceptable.

Compared to metformin, vildagliptin shows a more favourable profile when it comes to gastrointestinal side effects, whereas hypoglycaemic events were essentially similar and uncommon in both treatment groups. When compared to SU, vildagliptin treated patients report less hypoglycaemias and vildagliptin is essentially weight neutral whereas weight gain is observed in SU treated patients.

The CHMP safety concerns regarding treatment of patients with CHF and renal impairment have now been addressed. More data is now available in patients with CHF and no safety signals have emerged. It should be noted that the data presented only concerns patients with verified CHF. It should be taken into account that most likely the treated T2DM population do include a number of unidentified/undiagnosed patients with CHF. Accumulated data on CV risks with vildagliptin in the overall study population, now comprising over 11,500 patients, has also been provided and although

these data may not fully reflect the clinical situation and target population (due to short duration and a relatively low rate of patients at high CV risk), there are no signals of a negative effect of vildagliptin on CV safety.

Further to this, safety data in elderly patients have been assessed and the recommendation on cautious use of vildagliptin in this patient group has been removed from the SPC.

The additional safety data obtained after the initial approval of vildagliptin is considered sufficient in mitigating the concerns raised regarding the use of vildagliptin in patients with CHF and renal impairment. The warnings regarding patients with CHF included in section 4.4 of the SPC has been changed to only include patients with NYHA III-IV due to lack of data in this patient group.

In conclusion, the benefit risk balance for vildagliptin as monotherapy in patients intolerant to or with contraindications to metformin is considered positive by the CHMP.