HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

10 December 2008

GALVUS 50 mg, tablet
B/30 (CIP: 381 951-6)
B/60 (CIP: 383 221-5)
B/90 (CIP: 571 465-5)

Applicant: NOVARTIS PHARMA SAS

vildagliptin

ATC Code: A10BH02

List I

Date of marketing authorisation (centralised procedure): 26 September 2007, amended 25 January 2008

Reason for request:
Inclusion on the list of products reimbursed by National Insurance and for hospital use for presentations in boxes of 30 and 60
Inclusion on the list of products for hospital use for presentation in box of 90

1. PROPERTIES OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Vildagliptin

1.2. Background
Vildagliptin is an oral blood glucose lowering drug that belongs to the group of dipeptidylpeptidase-4 (DDP4) inhibitors, administration of which causes an increase in levels of incretin hormones.

1.3. Indications
“Vildagliptin is indicated in the treatment of type 2 diabetes mellitus:
as dual oral therapy in combination with
- metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin,
- a sulfonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulfonylurea and for whom metformin is inappropriate due to contraindications or intolerance,
- a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate. "

1.4. Dosage (see SPC)
"Adults:
When used in dual combination with metformin or a thiazolidinedione, the recommended daily dose of vildagliptin is 100mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening.

When used in dual combination with a sulphonylurea, the recommended dose of vildagliptin is 50mg once daily administered in the morning. In this patient population, vildagliptin 100mg daily was no more effective than vildagliptin 50mg once daily.

Doses higher than 100mg are not recommended.

The safety and efficacy of vildagliptin as triple oral therapy in combination with metformin and a thiazolidinedione or with metformin and a sulfonylurea has not been established.

Galvus can be administered with or without a meal (see also section 5.2).

Additional information on special populations
Renal impairment
No dose adjustment is required in patients with mild renal impairment (creatinine clearance ≥ 50 ml/min). The use of Galvus is not recommended in patients with moderate or severe renal impairment or in haemodialysis patients with end-stage renal disease (ESRD) (see also sections 4.4 Special Warnings and Precautions for Use, and 5.2 Pharmacokinetic Properties).

Hepatic impairment
Galvus should not be used in patients with hepatic impairment, including patients with pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST)> 3x the upper limit of normal (ULN) (see also sections 4.4 and 5.2).

Elderly (≥ 65 years):
No dose adjustments are necessary in elderly patients. Experience in patients aged 75 years and older is limited and caution should be exercised when treating this population (see also sections 5.1 and 5.2).

Paediatric population (< 18 years)

Galvus is not recommended for use in children and adolescents due to a lack of data on safety and efficacy. "

1.5. Special warnings and precautions for use (see SPC)[1]

"Renal impairment

There is limited experience in patients with moderate to severe renal impairment or in patients with ESRD on haemodialysis. Therefore, the use of Galvus is not recommended in these patients.

Hepatic impairment

Galvus should not be used in patients with hepatic impairment, including patients with pre-treatment ALT or AST> 3x ULN.

Liver enzyme monitoring

Rare cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function test results returned to normal after discontinuation of treatment. Liver function tests should be performed prior to the initiation of treatment with Galvus in order to know the patient's baseline value. Liver function should be monitored during treatment with Galvus at three-month intervals during the first year and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return(s) to normal.

Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of Galvus therapy is recommended.

Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Galvus.

Following withdrawal of treatment with Galvus and LFT normalisation, treatment with Galvus should not be reinitiated.

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.

Skin disorders

Skin lesions, including blistering and ulceration have been reported in extremities of monkeys in non-clinical toxicology studies (see section 5.3).

Although skin lesions were not observed at an increased incidence in clinical trials, there was limited experience in patients with diabetic skin complications. Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering or ulceration, is recommended. "

1 Special warnings and precautions for use, particularly for patients with hepatic impairment or heart failure, are not included in the SPC for sitagliptin (JANUVIA)

2. COMPARABLE MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

A: Alimentary tract and metabolism
A10: Drugs used in diabetes
A10B: Blood glucose lowering drugs, excluding insulin
A10BH: Dipeptidyl peptidase-4 (DPP4) inhibitors
A10BH02: vildagliptin

2.2. Medicines in the same therapeutic category

- JANUVIA 100 mg (sitagliptin)
- XELEVIA 100 mg (sitagliptin)

These products are indicated:

- "for patients with type 2 diabetes mellitus to improve glycaemic control, in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- for patients with type 2 diabetes for whom a PPARγ agonist is appropriate, in combination with a PPARγ agonist (thiazolidinedione), when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control . "[2]

2.3. Medicines with a similar therapeutic aim

Oral blood glucose lowering drugs that can be given in combination with metformin, a sulfonylurea or a glitazone, as part of dual oral therapy for diabetes, indicated:

- In type 2 diabetic patients not achieving adequate glycaemic control despite maximal tolerated dose of oral monotherapy with metformin:

- Sulfonylureas
- Glitazones
- Intestinal alpha-glucosidase inhibitors
- Glinide
- Parenteral incretin mimetics, exenatide (BYETTA)

- in type 2 diabetic patients with inadequate glycaemic control despite maximal tolerated dose of oral sulfonylurea monotherapy who show intolerance to metformin or for whom metformin is contraindicated:

- Glitazones
- Intestinal alpha-glucosidase inhibitors
- Glinide
- Parenteral incretin mimetics, exenatide (BYETTA)

- In type 2 diabetic patients not achieving adequate glycaemic control despite maximal tolerated dose of oral monotherapy with glitazone: Not applicable.

2 The indications for JANUVIA and XELEVIA are not identical to those for GALVUS. JANUVIA and XELEVIA are not indicated in combination with with sulfonylureas.

3. ANALYSIS OF AVAILABLE DATA

In support of its request, the applicant submitted:
- six comparative clinical studies,
- one analysis of safety data, using the combined results of the clinical trials,
- safety data taken from initial PSURs.

3.1. Efficacy results

Analysis of efficacy data for vildagliptin in combination with other oral blood glucose lowering drugs is based on 6 clinical studies submitted by the applicant:

- **three studies of vildagliptin (50 mg/day or 2x50 mg/day) versus placebo,**
  - **study 2303**, in combination with metformin in patients with inadequate glycaemia control on metformin alone
  - **study 2305**, in combination with glimepiride[3] in patients with inadequate glycaemia control on a sulfonylurea alone
  - **study 2304**, in combination with pioglitazone[4] in patients with inadequate glycaemia control on pioglitazone alone
- **one study comparing vildagliptin with pioglitazone,**
  - **study 2354**, in combination with metformin in patients with inadequate glycaemia control on metformin alone (not submitted to European registration authorities)
- **one study comparing vildagliptin with glimepiride,**
  - **study 2308IA**, in combination with metformin in patients with inadequate glycaemia control on metformin alone (not submitted to European registration authorities)
- **one study comparing vildagliptin with glitazones,**
  - **study 23119**, in combination with metformin in patients with inadequate glycaemia control on metformin alone (not submitted to European registration authorities)

3.1.1. Placebo-controlled studies: 2303[5] , 2305[6], 2304[7]

Objective and methodology:
The main aim of these three comparative, randomised, double-blind studies was to efficacy and safety of vildagliptin in combination with metformin or glimepiride or pioglitazone versus placebo, in patients with type 2 diabetes with inadequately controlled disease (HbA1c levels ≥7.5% and ≤11%) on metformin monotherapy (study 2303) or on glimepiride (study 2305) or on pioglitazone (study 2304).

Study 2303 treatments, in combination with metformin:
Five hundred and forty four patients (n=544), aged between 18 and 78 years, were randomised to receive one of the following three treatments for 24 weeks:
vildagliptin 50 mg/day once daily and metformin ≥ 1500 mg/day (n=177)
vildagliptin 100 mg/day, 50 mg twice daily and metformin ≥ 1500 mg/day (n=185)
- placebo and metformin ≥ 1500 mg/day (n=182).
Before randomisation, patients had been treated for at least 3 months with metformin, with a stable dose of ≥ 1500 mg/day for 4 weeks.

3 Group of sulfonylureas, glimepiride-based products: AMAREL and generics
4 Group of glitazones, pioglitazone-based products: ACTOS 15 mg and 30 mg
5 Bosi E *et al*. Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin. Diabetes Care. 2007; 30:890-895 et rapport d'étude
6 Garber AJ *et al*. Effects of vildagliptin on glucose control in patients with type 2 diabetes inadequately controlled with a sulphonylurea. Diabetes, Obes. Metab. 2008; 10: 1-10 and study report
7 Garber AJ *et al*. Vildagliptin in combination with pioglitazone improves glycaemic control in patients with type 2 diabetes failing thiazolidinedione monotherapy: a randomized, placebo-controlled study. Diabetes Obes. Metab. 2007;9:166-174.

Study 2305 treatments, in combination with glimepiride:
Five hundred and fifteen patients (n=515), aged between 18 and 80 years, were randomised to receive one of the following three treatments for 24 weeks:
- vildagliptin 50 mg/day once daily and glimepiride ≥ 4 mg/day (n=170),
- vildagliptin 100 mg/day, 50 mg twice daily and glimepiride ≥ 4mg/day (n=169),
- placebo and glimepiride ≥ 4mg/day (n=176).
Before randomisation, patients had been treated for at least 3 months with a sulfonylurea on a stable dose of (glimepiride ≥ 2 mg/day, glipizide ≥ 7.5 mg/day, glyburide ≥ 7.5 mg/day) for 4 weeks. It was possible to reduce the dose of glimepiride during the study, if hypoglycaemia occurred.

Study 2304 treatments, in combination with pioglitazone:
Four hundred and sixty three patients (n=463), aged between 18 and 80 years, were randomised to receive one of the following three treatments for 24 weeks:
- vildagliptin 50mg/day once daily and pioglitazone 45 mg/day (n=147),
- vildagliptin 100 mg/day, 50 mg twice daily and pioglitazone 45 mg/day (n=158),
- placebo and pioglitazone 45 mg/day (n=158).
Before randomisation, patients had been receiving a glitazone (pioglitazone > 30 mg or rosiglitazone > 4 mg) for three months, followed by pioglitazone 45 mg/day for 4 weeks, and this dose was continued for 24 weeks.

Inclusion criteria: Patients with type 2 diabetes aged 18 or over, with HbA1c levels of ≥ 7.5% and ≤ 11%, with no signs of renal impairment[8], recent history of heart disease[9] or liver impairment[10], and whose disease is inadequately controlled:
- study 2303: treatment with metformin monotherapy (≥1500 mg/day)
- study 2305: treatment with glimepiride monotherapy ≤ 4mg/day
- study 2304: treatment with pioglitazone monotherapy 45 mg/day

Primary endpoint: mean variation in HbA1c levels after 24 weeks of treatment versus placebo

Selected secondary endpoints:
- mean variation in fasting glycaemia at 24 weeks versus placebo
- percentage of patients with HbA1c ≤ 6.5% after 24 weeks of treatment

Results
The results of these studies (tables 1, 2 and 3) are based on analysis of patients with baseline HbA1c ≥ 7.4%, who received at least one dose of treatment, with a valid baseline HbA1c value and at lease one further valid measurement of HbA1c (modified ITT).
Mean baseline HbA1c levels were 8.4% (study 2303), 8.5% (study 2305) and 8.7% (study 2304).

8 Study 2303 (in combination with metformin): serum creatinine > 1.5 mg/dL (132 µmol/L) for men, > 1.4 mg/dL (123µmol/L) for women, or abnormal creatinine clearance; studies 2304 and 2305 (in combination with glimepiride and pioglitazone): serum creatinine > 2.5 mg/dL (220 µmol/L)
9 History of torsades de pointe, ventricular tachycardia or ventricular fibrillation, percutaneous coronary intervention during the past 3 months, or during the past 6 months: MI, coronary artery bypass or unstable angina, congestive heart failure requiring treatment; anti-arrhythmic treatment class I1, Ib, Ic or III; on ECG, second-degree atrioventricular block (Mobitz 1 and 2), third-degree atrioventricular block with prolonged QTc (> 500 ms)
10 Liver disease such as cirrhosis or chronic progressive hepatitis, significantly altered liver function tests: ALT or AST > 3 x ULN, bilirubin 1.3 x ULN at follow-up visit

Table 1 - Study 2303: in combination with metformin

	metformin in combination with		
	Vildagliptin 50 mg/day	Vildagliptin 2 x 50 mg/day	placebo
N (randomised)	177	185	182
N (modified ITT)	143	143	130
Mean age (years)*	54.2 ± 9.8 years (range 23 to 79 years)		
Mean baseline BMI (kg/m2) *	32.7 ± 5.4 kg/m2 (range 19 to 47.4)		
• **Change in HbA1c (%)**			
Mean baseline HbA1c (SD)	8.38 (0.08)	8.38 (0.09)	8.30 (0.08)
Change from baseline, adjusted mean (SD)	**-0.51** (0.10)	**-0.88** (0.10)	**+0.23** (0.10)
Difference versus placebo, adjusted mean (SD) 95% CI	**-0.73** (0.14) (-1.00, -0.47) **p** <0.001**	**-1.10** (0.14) (-1.37, -0.84) **p** <0.001**	
• Change in fasting blood glucose (g/L)			
Baseline fasting blood glucose (SD)	1. 74 (0.03)	1.78 (0.04)	1.81 (0.04)
Change from baseline, adjusted mean	-0.03 (0.04)	-0.18 (0.04)	+0.12 (0.04)
Difference versus placebo, adjusted mean 95% CI	-0.15 (0.05) (-0.25, -0.05) p=0.003	-0.30 (0.05) (-0.40, -0.20) p<0.001	
• % of patients with HbA1c ≤ 6.5%	9.2 % p=0.04	18.2% p<0.001	3.1%

** modified ITT population* ***using ANCOVA model*

mean dose of metformin: 2100 mg/day

Table 2 - Study 2305: in combination with glimepiride

	Glimepiride in combination with		
	Vildagliptin 50 mg/day	Vildagliptin 2 x 50 mg/day	placebo
N (randomised)	170	169	176
N (modified ITT)	132	132	144
Mean age (years)*	58.2 ± 10.7 years (range 26 to 82 years)		
Mean baseline BMI (kg/m2) *	31.3 ± 5.3 kg/m2 (range 21 to 47.4)		
• **Change in HbA1c (%)**			
Mean baseline HbA1c (SD)	8.53 (0.08)	8.55 (0.09)	8.53 (0.08)
Change from baseline, adjusted mean (SD)	**-0.58** (0.10)	**-0.63** (0.09)	**+0.07** (0.09)
Difference versus placebo, adjusted mean (SD) 95% CI	**-0.64** (0.13) (-0.90, -0.39) **p** <0.001**	**-0.70** (0.13) (-0.95, -0.44) **p** <0.001**	
• Change in fasting blood glucose (g/L)			
Baseline fasting blood glucose (SD)	1. 89 (0.05)	1.88 (0.04)	1.86 (0.04)
Change from baseline, adjusted mean (SD)	-0.06 (0.04)	-0.08 (0.04)	+0.03 (0.04)
Difference versus placebo, adjusted mean 95% CI	-0.09 (0.06) (-0.20, -0.02) p=0.118 NS	-0.11 (0.06) (-0.22, 0.00) p=0.056 NS	
• % of patients with HbA1c ≤ 6.5%	11.4 % p=0.137	13.6% p=0.041	6.3%

* modified ITT population **using ANCOVA model

dose of glimepiride reduced to 2 mg/day for 5 patients (1 in the vildagliptin 50 mg/day group, 3 in the vildagliptin 2 x 50 mg/day group and one in the placebo group)

Table 3 - Study 2304: in combination with pioglitazone

	Pioglitazone 45 mg/day in combination with		
	Vildagliptin 50 mg/day	Vildagliptin 2 x 50 mg/day	placebo
N (randomised)	147	158	158
N (modified ITT)	124	136	138
Mean age (years)*	54.3 ± 9.4 years (range 25 to 81 years)		
Mean baseline BMI (kg/m2) *	32.3 ± 5.5 kg/m2 (range 22 to 48)		
• **Change in HbA1c (%)**			
Mean baseline HbA1c (SD)	8.62 (0.09)	8.69 (0.11)	8.72 (0.10)
Change from baseline, adjusted mean (SD)	**-0.76** (0.10)	**-0.97** (0.10)	**-0.30** (0.10)
Difference versus placebo, adjusted mean (SD) 95% CI	**-0.46** (0.14) (-0.73, -0.19) **p** =0.001**	**-0.67** (0.14) (-0.94, -0.40) **p** <0.001**	
• Change in fasting blood glucose (g/L)			
Baseline fasting blood glucose (SD)	1. 86 (0.05)	1.79 (0.05)	1.81 (0.05)
Change from baseline, adjusted mean (SD)	-0.15 (0.04)	-0.20 (0.04)	-0.08 (0.04)
Difference versus placebo, adjusted mean 95% CI	-0.06 (0.05) (-0.17, 0.04) p=0.243 NS	-0.12 (0.05) (-0.23, -0.01) p=0.025	
• % of patients with HbA1c ≤ 6.5%	19.4 % p=0.090 NS	23.5% p=0.011	11.8%

** modified ITT population* ***using ANCOVA model*

For primary endpoint:
After 24 weeks of treatment, a greater reduction in HbA1c levels was seen:

- in patients on metformin + vildagliptin than in those on metformin monotherapy (difference between vildagliptin 2 x 50 mg/day and placebo: -1.10%, 95% CI [-1.37,-0.84]; p<0.001 in study 2303)
- in patients on glimepiride + vildagliptin than in those on glimepiride monotherapy (difference between vildagliptin 50 mg/day and placebo: -0.64 %, 95% CI [-0.90,-0.39]; p<0.001 in study 2305)
- in patients on pioglitazone + vildagliptin than in those on pioglitazone monotherapy (difference between vildagliptin 2 x 50 mg/day and placebo: -0.67%, 95% CI [-0.94,-0.40]; p<0.001 in study 2304).

For secondary efficacy endpoints:

Fasting glycaemia:

- A greater reduction in fasting glycaemia was seen:

- in patients receiving metformin + vildagliptin 2 x 50 mg/day than in those treated with metformin monotherapy: -0.18 g/L versus +0.12 g/L (difference between vildagliptin 2 x 50 mg/day and placebo: -0.30 g/L, 95% CI [-0.40,-0.20]; p<0.001) in study 2303,
- in patients receiving pioglitazone + vildagliptin 2 x 50 mg/day than in those treated with pioglitazone monotherapy: -0.20 g/L versus -0.08 g/L (difference between vildagliptin 2 x 50 mg/day and placebo: -0.12 g/L, 95% CI [-0.23,-0.01]; p<0.025) in study 2304,

- variation in fasting glycaemia was similar in the groups receiving glimepiride + vildagliptin and glimepiride alone in study 2305.

Percentage of patients with HbA1c ≤ 6.5%

- This was greater:

- in the group treated with metformin + vildagliptin 2 x 50 mg/day than in the group receiving metformin monotherapy (18.2% versus 3.1%; p<0.001) in study 2303,
- in the group treated with pioglitazone + vildagliptin 2 x 50 mg/day than in the group receiving pioglitazone monotherapy (23.5% versus 11.8%; p<0.011) in study 2304,

- There was no difference between the groups treated with glimepiride + vildagliptin 50 mg/day and glimepiride in study 2305.

3.1.2 Study versus active comparator: combination of metformin + pioglitazone, study 2354 [11]

Objective and methodology:
The main objective of this randomised double-blind study was to demonstrate the non-inferiority of the combination of metformin + vildagliptin in comparison with metformin + pioglitazone in terms of reduction in HbA1c in patients with type 2 diabetes aged between 187 and 77 years old whose disease was inadequately controlled (HbA1c ≥ 7.5% and ≤ 11%) by a stable dose of metformin monotherapy ≥ 1500 mg/day[12]. Among the non-inclusion criteria were heart disease[13], renal impairment[14] and liver disease[15].

11 study report, and Bolli G *et al.* Efficacy and tolerability of vildagliptin vs pioglitazone when added to metformin : a 24 week, randomised, double blind study. Diabetes, Obes. And Metab. 2008;10 :82-90
12 treated with metformin for 3 months, at a dose of 1500 mg/day for at least 4 weeks
13 Torsades de pointe, ventricular tachycardia, ventricular fibrillation, coronary intervention in the last 3 months, within the last 6 months myocardial infarction, aortocoronary bypass, unstable angina, CVA, heart failure (NYHA class I-IV), 2nd and 3rd degree AV block, prolonged QT interval (>500 ms), treatment with class Ia, Ib, Ic or III antiarrhythmic agents
14 serum creatinine ≥ 132 micromol/L for men and ≥ 123 micromol/L for women
15 liver disease such as cirrhosis or active chronic hepatitis liver failure, ALT or AST >2.5 x upper limit of normal.

Administration schedule: 576 patients were randomised and received one of the following for 24 weeks:
- vildagliptin 50mg twice daily in combination with metformin ≥ 1500 mg/day (n=295) or
- pioglitazone 30 mg/day in one dose in combination with metformin ≥ 1500 mg/day (n=281)

Primary endpoint[16] : mean variation in HbA1c levels after 24 weeks of treatment in comparison with baseline

The vildagliptin/metformin combination would be considered to be non-inferior to the combination of pioglitazone/metformin if the upper limit of the 95% confidence interval of the difference between the two combinations (vildagliptin/metformin - pioglitazone/metformin) was less then 0.4% (the non-inferiority threshold was subsequently set at 0.3%, following an amendment to the protocol).

Selected secondary endpoints: after 24 weeks of treatment, fasting glycaemia and percentage of patients with HbA1c ≤ 6.5%

Results:
Results as presented in table 4 are based on the per-protocol analysis. Thirty three patients (11.2%) in the vildagliptin group (n=295) and 37 (13.2%) in the pioglitazone group (n=281) stopped taking the treatment because of lack of efficacy (2.7% versus 2.8%), adverse events (2.7% versus 3.2%) or for other reasons.[17]

Mean baseline HbA1c was around 8.4%; 42.2% of patients in the randomised population had baseline HbA1c of ≤ 8% and 24.7% had values of > 9%.

Table 4 - Study 2354: metformin/vildagliptin versus metformin/pioglitazone

	Metformin in combination with	
	vildagliptin 2 x 50 mg/day	pioglitazone 30 mg/day
N (randomised)	295	281
N (per-protocol)	264 (89.5%)	246 (87.5%)
Mean age (years)*	56.6 ± 9.5 years (range 29 to 77 years)	
Mean initial BMI (kg/m2) *	32.1 ± 5.4 kg/m2 (range 22 to 46.8)	
• **Change in HbA1c (in %) with respect to baseline**		
Mean baseline HbA1c (SD)	8.41 (0.06)	8.40 (0.06)
Change from baseline, adjusted mean (SD)	**-0.88** (0.05)	**-0.98** (0.06)
Difference between groups, adjusted mean (95% CI)	**-0.10** (0.08) (-0.05, -0.26)**	
• Mean change in fasting glycaemia (g/L)		
Mean glycaemia on inclusion (SD)	1.97 (0.03)	1.98 (0.03)
Change from baseline, adjusted mean (SD)	-0.24 (0.02)	-0.37 (0.03)
Difference between groups, adjusted mean (95% CI)	0.13 *** (0.06, 0.20)	
• % of patients with HbA1c ≤ 6.5% after 24 weeks	19.7%	17.9%

** randomised population **ANCOVA model *** non-inferiority margin 0.6 mmol/L, or 0.108 g/L (1 mmol/L=18.02 mg/dL)*
mean dose of metformin throughout the study: 2020 mg/day (452), 60.7% of patients in the vildagliptin group and 57.7% of patients in the pioglitazone group received doses of metformin of ≥ 2000 mg/day.

For the primary endpoint: as the upper limit of the 95% confidence interval of the difference between the two combinations (vildagliptin/metformin - pioglitazone/metformin) was lower than the set non-inferiority threshold (0.3%), it was established that vildagliptin/metformin was non-inferior to pioglitazone/metformin.

Secondary efficacy endpoints: no difference was observed in the percentage of patients with Hba1c levels ≤ 6.5% at 24 weeks, for either of the two treatment combinations.
It was not established that metformin/vildagliptin was non-inferior to metformin/pioglitazone in terms of reduction in fasting glycaemia.

16 Amendment to protocol: blind was lifted at 24 weeks.
17 Withdrawal of consent: 2.4% vs 5%, protocol violation 1.4% vs 0.4%, lost to follow-up 1.7% vs 1.4%, administrative problems 0.3% vs 0.4%.

3.1.3. Study versus active comparator: combination of metformin + glimepiride, study 2308IA interim analysis at 1 year (in press)

Primary endpoint: to demonstrate long-term efficacy and safety of the combination metformin + vildagliptin (GALVUS) in comparison with the combination metformin + glimepiride in patients with type 2 diabetes whose disease is inadequately controlled by metformin monotherapy (HbA1c > 6.5% and ≤ 8.5%) over a treatment period of up to 5 years. The primary endpoint of this study was to evaluate failure of glycaemic control (defined as a HbA1c level of >8.0%).

The protocol for this study contained a provision for a 1-year interim analysis[18], the aim of which was to demonstrate non-inferiority of the combination metformin + vildagliptin in comparison with the combination metformin + glimepiride in 2789 patients (1396 in the metformin + vildagliptin group, 1393 in the metformin + glimepiride group) in terms of reduction in HbA1c.

Method: phase III, randomised, comparative, double-blind study.

Inclusion criteria: patients with type 2 diabetes aged between 18 and 73, whose disease is inadequately controlled (HbA1c levels > 6.5% and ≤ 8.5%) on metformin monotherapy at a stable dose of ≥ 1500 mg/day[19] with BMI between 22 and 45 kg/m^2.

Note: the inclusion criteria are similar to the other studies, apart from HbA1c levels. It is of note that among the non-inclusion criteria were patients with heart disease[20], renal impairment[21] and liver disease[22]. As a result, there were very few cardiac, renal or liver complications among the included patients.

Administration schedule:
Patients who were treated with a stable dose of metformin (≥ 1500 mg/day) were randomised to receive either vildagliptin at a dose of 50 mg twice daily, or glimepiride. The initial glimepiride dose was 2 mg/day. This dose was then gradually titrated step by step, up to a maximum of 6 mg/day. The mean daily glimepiride dose at 1 year was 4.5 mg/day.

Primary endpoint:
Change in HbA1c between inclusion and end of study (1 year)

The combination metformin + vildagliptin would be considered to be non-inferior to the combination metformin + glimepiride if the upper limit of the 97.5% confidence interval of the difference in change in Hba1c levels between the two treatments (metformin/vildagliptin - metformin/glimepiride) was less than 0.3%.

Note: the choice of comparator is relevant (the metformin/sulfonylurea combination is the gold standard dual therapy). Glimepiride and metformin were used at the optimal dose as recommended in the marketing authorisation for each drug. The non-inferiority threshold chosen was 0.3%, which is more restrictive than the threshold that is usually used (0.4%).

18 The protocol stated that this one-year interim analysis should be carried out as soon at 2800 patients had completed 52 weeks of treatment in the primary study.
A method for controlling inflation in alpha risk due to multiple comparisons was implemented.
19 treated with metformin for 3 months, at a dose of 1500 mg/day for at least 4 weeks
20 Torsades de pointe, ventricular tachycardia, ventricular fibrillation, coronary intervention in the last 3 months, within the last 6 months myocardial infarction, aortocoronary bypass, unstable angina, CVA, heart failure (NYHA class I-IV), 2nd and 3rd degree AV block, prolonged QT interval (>500 ms), treatment with class Ia, Ib, Ic or III antiarrhythmic agents
21 serum creatinine ≥ 132 micromol/L for men and ≥ 123 micromol/L for women
22 liver disease such as cirrhosis or active chronic hepatitis liver failure, ALT or AST >2.5 x upper limit of normal.

Secondary endpoints:

- Mean variation in fasting glycaemia after 1 year of treatment
- Weight change
- Percentage of patients who responded to treatment, defined as the percentage of patients reaching a predefined target HbA1c value at 1 year (HbA1c < 7%, HbA1c ≤ 6.5%, HbA1c ≤ 6% and reduction in HbA1c from baseline of ≥ 0.5% and ≥ 0.7%)
- Coefficient of glycaemic control failure between the 6th and 12th months of treatment (this coefficient represents the slope of the HbA1c variation curve; no conclusion can be drawn from this analysis).

Results: (ITT Population)

On inclusion, patient characteristics were similar. Patients:

- had a mean age of 57.5 years (25% of patients were 65 or over),
- were mostly obese (mean BMI 31.8 kg/m2, around 68% of patients had a BMI of ≥ 30 kg/m2, 26% had a BMI of ≥ 35 kg/m2).

Time since diagnosis of diabetes was 5.7 years, and patients had been treated with metformin for a mean period of 3 years, with a mean dose of 1898 mg/day.

At inclusion, the mean HbA1c level was 7.3%. The majority of patients (86%) had HbA1c of ≤ 8%.

Primary endpoint:

Table 5: change in HbA1c levels (PP population):

Treatment groups	n	Initial mean HbA1c level (SD)	Change in adjusted mean HbA1c level (SD)	Difference/ comparator mean (SD)	97.5% CI
vildagliptin + metformin	1118	7.33 (0.02)	-0.44 (0.02)	0.09 (0.03)	(0.02, 0.16)
glimepiride + metformin	1072	7.36 (0.02)	-0.53 (0.02)		

The upper limit of the 97.5% confidence interval was less than the set threshold. In this study, the metformin + vildagliptin combination was non-inferior to the metformin + glimepiride combination.

These results are confirmed in the ITT population.

Subgroup analyses (by age, BMI and baseline HbA1c), as planned for in the protocol, were provided by the applicant. As no statistical tests had been carried out, the results of these exploratory subgroup analyses will not be described here.

Secondary endpoints:

- Mean variation in fasting glycaemia after 1 year of treatment:

no difference between the two treatment groups was observed.

- Weight change:

After 1 year of treatment, the weight of patients in the metformin + vildagliptin group fell by 0.23 kg, and that of the patients in the metformin + glimepiride group increased by 1.56 kg (a difference of 1.79 kg, 95% CI [-2.10; -1.48], p<0.001).

- Percentage of patients who responded to treatment, defined as the percentage of patients reaching a predefined target HbA1c value at 1 year (HbA1c < 7%, HbA1c ≤ 6.5%, HbA1c ≤ 6% and reduction in HbA1c from baseline of ≥ 0.5% and ≥ 0.7%):

Table 6:

	vildagliptin + metformin n (%)	**glimepiride + metformin (%)**	**p**
Per-protocol population	N = 1118	N = 1072	
A least one of the criteria	712 (63.7)	716 (66.8)	NS
HbA1c < 7%	427/789 (54.)	415/748 (55.)	NS
HbA1c ≤ 6.5%	381/1043 (36.5)	440/1014 (43.4)	0.001
HbA1c ≤ 6.0%	134/1116 (12.0)	174/1069 (16.3)	0.004
Reduction in HbA1c ≥ 0.7%	452 (40.4)	502 (46.8)	0.003
Reduction in HbA1c ≥ 0.5%	602 (53.8)	621 (57.9)	NS
ITT Population	N = 1359	N = 1321	
A least one of the criteria	820 (60.4)	843 (64.0)	NS
HbA1c < 7%	477/920 (51.8)	477/873 (54.6)	NS
HbA1c ≤ 6.5%	425/1230 (34.6)	497/1207 (41.2)	0.001
HbA1c ≤ 6.0%	160/1354 (11.8)	208/1311 (15.9)	0.002
Reduction in HbA1c ≥ 0.7%	501 (36.9)	563 (42.7)	0.002
Reduction in HbA1c ≥ 0.5%	687 (50.6)	718 (54.5)	0.044

The aim of the dual therapy stage is to bring HbA1c levels down to below 6.5%. This objective was reached by 36.5% of the patients in the metformin + vildagliptin group compared with 34.4% of patients in the metformin + glimepiride group. This difference was statistically significant.

3.1.4. Study versus active comparator: combination of metformin + glitazone, study US GALIANT-23119 (in press):

This randomised, open-label 12-week study compared the combination metformin + vildagliptin, administered at a dose of 100 mg once daily, with the combination of metformin + glitazone (pioglitazone in 74% of cases) in 2664 patients with type 2 diabetes whose disease is inadequately controlled by metformin monotherapy, followed up in community practice in the United States.
This study cannot be taken into account by the Committee, because:

- its duration was too short;
- it was only carried out in the United States, which causes problems with transposition of data;
- in particular, it involved vildagliptin administered at a dose of 100 mg once daily, which does not conform to the European SPC. Marketing authorisation was not granted to GALVUS 100 mg in Europe, given its poor safety profile, particularly in terms of liver function, which was observed at this dose in clinical trials.

3.2. Safety data

Safety of vildagliptin was estimated using data from:
- monotherapy studies (off-label) with duration ≥ 12 and ≤ 52 weeks, which are brought together in a combined database of 8 clinical trials (phase II (2202, 2205) and phase III (2329, 2301, 2384, 2327, 2309, 2355 - one arm), which included a total of 2264 patients
- studies involving combinations of treatments, with duration ≥ 12 and ≤ 52 weeks, which are brought together in a second combined database (phase II (2204, 2204^{E}1, phase III 2303) and 4 clinical studies (2304, 2305, 2311 (off-label in combination with insulin) 2355 - two of the arms), which included a total of 1520 patients

Evaluation of liver safety is taken from an additional dossier containing all controlled clinical studies in the initial dossier, with additional liver data from clinical studies that finished more recently (July 2007), long-term safety data (from study extensions with duration ≥ 52 weeks), interim analyses of current studies and notifications from countries in which the product is already being marketed. A total of around 7400 patients treated with GALVUS were taken into account when assessing liver safety.

3.2.1. According to the SPC (section 4.8)

Safety data were obtained from a total of 3,784 patients exposed to vildagliptin at a daily dose of 50mg (once daily) or 100mg [23] in controlled trials of at least 12 weeks duration[24]. Of these patients, 2,264 patients received vildagliptin as monotherapy and 1,520 patients received vildagliptin in combination with another medicinal product.

Rare cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function test results returned to normal after discontinuation of treatment. In data from controlled monotherapy and add-on therapy trials of up to 24 weeks in duration, the incidence of ALT or AST elevations ≥ 3x ULN (classified as present on at least 2 consecutive measurements or at the final on-treatment visit) was 0.2%, 0.3% and 0.2% for vildagliptin 50 mg once daily, vildagliptin 50 mg twice daily and all comparators, respectively. These elevations in transaminases were generally asymptomatic, non-progressive in nature and not associated with cholestasis or jaundice.

Rare cases of angioedema have been reported on vildagliptin at a similar rate to controls. A greater proportion of cases were reported when vildagliptin was administered in combination with an angiotensin converting enzyme inhibitor (ACE-Inhibitor). The majority of events were mild in severity and resolved with ongoing vildagliptin treatment.

Combination with metformin
In controlled clinical trials with the combination of vildagliptin 100mg daily + metformin, no withdrawal due to adverse reactions was reported in either the vildagliptin 100mg daily + metformin or the placebo + metformin treatment groups.
In clinical trials, the incidence of hypoglycaemia was common in patients receiving vildagliptin 100mg daily in combination with metformin (1%) and uncommon in patients receiving placebo + metformin (0.4%). No severe hypoglycaemic events were reported in the vildagliptin arms.

In clinical trials, weight did not change from baseline when vildagliptin 100mg daily was added to metformin (+0.2 kg and -1.0 kg for vildagliptin and placebo, respectively).
The most commonly reported adverse effects (≥1/100, <1/10) in double-blind studies (n=208)[25] were tremor, headache, dizziness and nausea.

50mg twice daily or 100mg once daily

24 274 patients were exposed to treatment for ≥ 52 weeks.

25 Pooled data from studies 2303 (phase III) and 2204 (phase II) n=208

Combination with a sulfonylurea
In controlled clinical trials with the combination of vildagliptin 50mg + a sulfonylurea, the overall incidence of withdrawals due to adverse reactions was 0.6% in the vildagliptin 50mg + sulfonylurea vs 0% in the placebo + sulfonylurea treatment group.

In clinical trials, the incidence of hypoglycaemia when vildagliptin 50mg once daily was added to glimepiride was 1.2% versus 0.6% for placebo + glimepiride. No severe hypoglycaemic episodes were reported in the vildagliptin arms.

In clinical trials, weight did not change from baseline when vildagliptin 50mg daily was added to glimepiride (-0.1 kg and -0.4 kg for vildagliptin and placebo, respectively).

The most commonly reported adverse effects (≥1/100, <1/10) in studies on patients who had received 50 mg vildagliptin in double-blind studies (n=170) were tremor, headache, dizziness and asthenia.

Combination with a thiazolidinedione
In controlled clinical trials with the combination of vildagliptin 100mg daily+ a thiazolidinedione, no withdrawal due to adverse reactions was reported in either the vildagliptin 100mg daily + thiazolidinedione or the placebo + thiazolidinedione treatment groups.

In clinical trials, the incidence of hypoglycaemia was uncommon in patients receiving vildagliptin + pioglitazone (0.6%) but common in patients receiving placebo + pioglitazone (1.9%).

No severe hypoglycaemic events were reported in the vildagliptin arms.
In the pioglitazone add-on study, the absolute weight increases with placebo, Galvus 100mg daily were 1.4 and 2.7 kg, respectively.

The incidence of peripheral oedema when vildagliptin 100mg daily was added to a maximum dose of background pioglitazone (45 mg once daily) was 7.0%, compared to 2.5% for background pioglitazone alone.

The most commonly reported adverse effects (≥1/100, <1/10) in studies on patients who had received 100 mg per day vildagliptin in combination with a thiazolidinedione (n=158) were weight gain and peripheral oedema. "

3.2.2. Study 2354: vildagliptin/metformin versus pioglitazone/metformin, not registered with trial registration authorities

Adverse events were observed in 60% of the patients in the vildagliptin group (n=295) versus 56.4% of those in the pioglitazone group (n=281).
The most commonly observed adverse events in the vildagliptin group were:
gastrointestinal problems (15.9% versus 8.9%), including diarrhoea (3.4% vs 2.9%), constipation (3.1% vs 1.1%), dyspepsia (2.4% vs 0.7%), nausea (4.8% vs 2.1%) and general problems: 14.6% vs 11.1%, including oedema (8.8% vs 6.1%), headache (6.1% vs 5.7%).
The following emerged in the vildagliptin + pioglitazone group: skin problems (8.1% vs 6.1%), heart problems (3.7% vs 2.5%).
Adverse effects that were considered to be linked to treatment in the vildagliptin versus the pioglitazone groups (13.2% vs 10.7%), were mainly:
- gastrointestinal problems: 5.1% versus 2.9%
- oedema: 4.1% versus 2.9%
- skin disorders: 1% versus 1.4%
Three episodes of hypoglycaemia[26]were reported in 1 patient in the vildagliptin group.

26 grade 1: the patient was capable of self-treatment and plasma glucose was <3.1 mmol/L

Patient weight was observed to be stable in the vildagliptin group (+0.3 kg, initial mean weight 91.6 kg), while a weight increase was noted in the pioglitazone group (+1.9 kg, initial mean weight 92 kg), p<0.001[27].
Eighteen patients (9 in each group) stopped treatment.

3.2.3. Study 2308IA: vildagliptin/metformin versus glimepiride/metformin, not registered with trial registration authorities

Adverse events were reported in 74.5% of the patients in the metformin + vildagliptin group compared with 81.1% of patients in the metformin + glimepiride group.

The adverse events that were more common in the metformin + vildagliptin group than in the metformin + glimepiride group were: flu syndrome (5.7% vs 4.3%), diarrhoea (5.5% vs 5.1%) and back pain 5.4% vs 5.1).

In the group treated with metformin + vildagliptin, 1.7% of patients (23/1389) had hypoglycaemia (39 hypoglycaemic episodes in total) compared with 16.2% of patients (224/1383) treated with metformin + glimepiride (554 hypoglycaemic episodes in total).
No episodes of severe hypoglycaemia were observed in the metformin + vildagliptin group, while 10 episodes of severe hypoglycaemia were observed in the metformin + glimepiride group.
11 patients stopped treatment in the metformin + glimepiride group because of hypoglycaemia, compared with none in the metformin vildagliptin group.

The incidence of abnormalities in liver function tests was similar in the two treatment groups (16 patients in the metformin + vildagliptin group and 12 patients in the metformin + glimepiride group had ALT or AST ≥ 2 x ULN).

8% of patients (111/1383) in the metformin + glimepiride group stopped treatment because of adverse effects , compared with 5% of patients in the metformin + vildagliptin group (69/1389).

3.2.4 additional safety data

Combined analysis of safety data for all clinical trials has been updated to include results of new studies (this analysis involves more than 6718 patients treated with vildagliptin as monotherapy or combination).

We also have the main conclusions from the first two PSURs, with cumulative data collected between 14 February 2007 and 29 February 2008. This involves 10,078 patients who received GALVUS in clinical trials between February 2007-2008, 62,807 patients who received GALVUS in post-marketing studies and 14,842 patient-years of exposure to the marketed product during this period (14 February 2007 to 29 February 2008).

- Cardiovascular safety:

Conduction and heart rhythm disorders were observed in 1.1% of patients treated with GALVUS. This incidence was comparable with the placebo group (1.4%) and with comparators (1.3%). The incidence of 1st degree atrioventricular block was 0.3% on GALVUS vs 0.4% on placebo and 0.3% on comparators. The incidence of cardiovascular, cerebrovascular and peripheral vascular events was not greater than that in the placebo and comparator groups.
The incidence of cardiac failure was 0.20% in patients receiving GALVUS, 0.23% in placebo groups and 0.25% in comparator groups.

- Infection risk:

The current clinical data do not suggest any increased risk of infection or severe infection.

27 adjusted mean, Δ between treatments: -1.6 kg, 95% CI [-2.1,-1.1]; p<0.001 according to ANCOVA model

- Skin safety:

Cutaneous and subcutaneous adverse events were reported in 7.4% of patients treated with GALVUS (all doses), 8.6% of patients in placebo groups and 10.9% of patients in comparator groups. 98% of lesions observed in patients treated with GALVUS were mild to moderate (hyperhidrosis being the most commonly reported adverse event).

Cumulative data from PSURs did not identify:

- any new cases of treatment-linked liver dysfunction;
- any new specific indications of a risk of serious infection;
- any increase in the risk of angioedema (45 cases were reported, and the incidence of angioedema was increased in those taking an ACE inhibitor).

3.3. Conclusion:

- **In terms of efficacy**, the effect of vildagliptin (at a dose of 50 mg once daily or 50 mg twice daily) on reduction in HbA1c was evaluated after 24 weeks of treatment in combination with metformin or glimepiride or pioglitazone in patients with type 2 diabetes whose disease is inadequately controlled by metformin ≥ 1500 mg/day (studies 2303 and 2354) or by glimepiride ≤ 4 mg/day (study 2305) or by pioglitazone 45 mg/day (study 2304). Among non-inclusion criteria were, in particular, signs of renal impairment, hepatic impairment and history of heart disease.

In combination with metformin, add-on of vildagliptin 50 mg twice daily reduced Hba1c levels in comparison to continued treatment with metformin monotherapy (difference between vildagliptin 50 mg twice daily and placebo: -1.10%, 95% CI [-1.37,-0.84]; p<0.001, baseline 8.4%).

In combination with glimepiride, add-on of vildagliptin 50 mg once daily reduced Hba1c levels in comparison to continued treatment with glimepiride monotherapy (difference between vildagliptin 50 mg once daily and placebo: -0.64 %, 95% CI [-0.90,-0.39]; p<0.001, baseline 8.5%). Given the similar reductions in HbA1c levels on vildagliptin 50 mg once daily and vildagliptin 50 mg twice daily, and the more favourable safety profile of the lower dose in terms of hypoglycaemia and weight chance, vildagliptin 50 mg/day is recommended in combination with a sulfonylurea.
The study was not specifically carried out on patients in whom metformin is contraindicated or poorly tolerated.

In combination with pioglitazone, add-on of vildagliptin 50 mg twice daily reduced Hba1c levels in comparison to continued treatment with pioglitazone 45 mg/day (difference between vildagliptin 50 mg twice daily and placebo: -0.67%, 95% CI [-0.94,-0.40]; p<0.001, baseline 8.7%).

In study 2354 versus active comparator (pioglitazone at the non-optimal dose of 30 mg/day) in combination with metformin, add-on of vildagliptin 50 mg twice daily was non-inferior to pioglitazone in terms of reduction in HbA1c levels (-0.88% vs -0.98%, difference between treatments -0.10%, 95% CI [-0.05, -0.26], mean baseline 8.4%).

In study 2308IA, the primary endpoint was to demonstrate long-term efficacy and safety of the combination metformin + vildagliptin in comparison with the combination metformin + glimepiride in patients with type 2 diabetes whose disease is inadequately controlled by metformin monotherapy (HbA1c > 6.5% and ≤ 8.5%) over a treatment period of up to 5 years. The protocol for this study contained a provision for a 1-year interim analysis, the aim of which was to demonstrate non-inferiority of the combination metformin + vildagliptin in comparison with the combination metformin + glimepiride in 2789 patients (1396 in the metformin + vildagliptin group, 1393 in the metformin + glimepiride group) in terms of reduction in HbA1c.
The upper limit of the 97.5% confidence interval was less than the set threshold. The metformin + vildagliptin combination was non-inferior to the metformin + glimepiride combination.
Nevertheless, it is important to note that a statistically significant difference was observed in terms of the therapeutic endpoint (HbA1c < 6.5%) with the metformin + glimepiride combination performing better than the metformin + vildagliptin combination.
No difference was observed between the two treatment groups in terms of mean change in fasting glycaemia.
The information provided by this 1-year interim analysis is not optimal in comparison with the expected definitive results.

In four of the five studies, the reduction in HbA1c levels was of the order of -0.7%. This level of efficacy was also observed by the authors of a meta-analysis[28] that looked at 29 trials of the efficacy and safety of incretin mimetics, which concluded that these products had modest efficacy (reduction in HbA1c levels -0.74% versus placebo and DPP-4 inhibitors were non-inferior to active comparators)[29].

- **In terms of safety**, in combination with metformin, in studies 2303 and 2204 versus placebo, the most commonly observed adverse effects in the vildagliptin group were nervous system (tremor, headache, dizziness) and gastrointestinal problems (nausea). The same effects, with the addition of asthenia, were observed with the combination involving glimepiride, in study 2305 versus placebo. In combination with pioglitazone, in study 2304 versus placebo, weight gain and peripheral oedema were more commonly in the vildagliptin groups.

The number of episodes of hypoglycaemia observed was similar in the placebo and vildagliptin groups in studies 2303 and 2305.

Weight changes on vildagliptin 50 mg/day were similar to those observed on placebo in studies 2303, 2305 and 2304. On vildagliptin 50 mg twice daily, mean changes in weight of +1.2 kg kg (study 2303), +1.3 kg (study 2304) and +1.7 kg (study 2305) were observed.

In study 2354, patient weight remained stable on metformin/vildagliptin, while a weight increase was noted with the metformin/pioglitazone combination. The vildagliptin was observed to have a greater percentage of patients with peripheral oedema than the pioglitazone group.
In study 2308IA, the number of patients with hypoglycaemia was greater in the metformin + glimepiride group (224/1383) than in the metformin + vildagliptin group (23/1389). No episodes of severe hypoglycaemia were observed in the metformin + vildagliptin group, while 10 episodes of severe hypoglycaemia were observed in the metformin + glimepiride group.
It is useful to note that included patients had low levels of HbA1c and that titration of glimepiride seems to have been rapid, and this could have led to an increase in hypoglycaemia in the metformin + glimepiride group.

28 Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. Renee E. Amori *et al*. JAMA 2007; 298 (2): 194-206

29 Mean variation in HbA1c levels observed were:
- -1 to -1.5% with metformin
- -1 to -1.5% with sulfonylureas
- -1% with glitazones
- -0.8% with glinides
- -0.5 to 1% with alphaglucosidase inhibitors
-

After 1 year of treatment, the weight of patients in the metformin + vildagliptin group fell by 0.23 kg, and that of the patients in the metformin + glimepiride group increased by 1.56 kg (a difference of 1.79 kg, 95% CI [-2.10; -1.48], p<0.001).

An updated analysis of safety data, carried out on combined data from controlled trials of monotherapies and combinations involving around 7000 patients treated with GALVUS showed no increase in the risk of cardiovascular or skin problems, angioedema or infection, in comparison with placebo or comparators. Cumulative data from PSURs have identified no new cases of treatment-linked hepatic impairment, no new signs of a risk of serious infection or increased risk of angioedema. However, doubts as to the safety profile of GALVUS persist.

The European risk management plan includes, in particular, careful monitoring of skin problems (with or without oedema or vascular disorders), hepatic disorders (including transaminases), angioedema, severe infection, cardiac conduction disorders and patients with moderate to severe renal impairment or who have reduced cardiac function.

No direct comparisons versus other dual oral diabetes therapies (including, in particular, glinides or alphaglucosidase inhibitors) that would enable a conclusion to be drawn as to the relative roles of sulfonylurea + vildagliptin and glitazones + vildagliptin. There are no available studies that compare:

- the combination glitazone + vildagliptin or sulfonylurea + vildagliptin with sulfonylurea + glitazone
- the combination sulfonylurea + vildagliptin with alphaglucosidase inhibitors + sulfonylurea.

No study has shown that vildagliptin in combination with an oral blood glucose lowering drug is superior to one of the gold-standard oral blood glucose lowering drugs.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Type 2 diabetes mellitus is a chronic disease with potentially serious complications.
GALVUS is used for the treatment of hyperglycaemia.
Considering the available data, the efficacy/adverse effects ratio of GALVUS in its indications as a dual oral therapy is classified as medium, given:
- the observed effect on reduction in HbA1c levels;
- the safety profile, particularly in terms of skin and cardiac problems, which is poorly-defined given the non-severe characteristics of the patients who were studied, and the results of available studies;
- uncertainties as to liver safety.

There are other dual oral therapy alternatives.
Given the existence of these therapeutic alternatives and the medium efficacy/adverse effects ratio, the role of GALVUS in the treatment strategy for type 2 diabetes is limited.

Public Health Benefit:
The public health burden of type 2 diabetes is high. The burden corresponding to the subpopulation of patients with the indications for treatment with GALVUS is moderate.
Improved therapeutic management of patients with type 2 diabetes is a public health need.

Given the results of studies versus active comparators, no additional impact is expected from GALVUS + metformin in comparison with the combinations metformin + thiozolidinedione and metformin + glimepiride.
It is not certain that experimental data can be transposed to clinical practice.
In addition, the impact of GALVUS (in combination with a sulphonylurea or a thiazolidinedione in comparison with currently available dual oral therapies) on glycaemic control and morbidity and mortality linked to type 2 diabetes cannot be assessed using the available data.

With the current state of knowledge, it is difficult to acknowledge that GALVUS will be able to meet the public health need, particularly since GALVUS can only be used in a very restricted patient population, considering the numerous special warnings and precautions for use regarding this product.
Accordingly, GALVUS is not expected to benefit public health.

The actual benefit of GALVUS is substantial.

4.2. Improvement in actual benefit

GALVUS does not provide an improvement in actual benefit (IAB V) in the management of patients with type 2 diabetes.

4.3. Therapeutic use

The objectives of therapeutic management are:

- glycaemic control: control of HbA1c;
- control of associated risk factors.

According to the guideline "Medication for type 2 diabetes" published by Afssaps and HAS in November 2006, the initial treatment of type 2 diabetes is based on an assessment and realistic changes in lifestyle habits (diet and exercise). The adoption of an active lifestyle and nutritional planning are essential interventions at all stages of diabetes management.
Oral blood glucose lowering drugs are prescribed when diet and lifestyle changes (DLC) are no longer sufficient to control blood glucose levels: HbA1c > 6%. There are 4 classes: metformin, intestinal alpha-glucosidase inhibitors (AGI), insulin secretors, glitazones.

At the dual oral therapy stage (when monotherapy fails: HbA1C > 6.5% after 6 months of one of the monotherapies at maximum dose), one of the following dual oral therapies may be proposed:
- metformin + insulin secretor (sulfonylurea or glinide)
- metformin + glitazone
- metformin + alphaglucosidase inhibitor
- insulin secretor + glitazone, in the case of clear and persistent intolerance to metformin or if metformin is contraindicated.
- or insulin secretor + alphaglucosidase inhibitor (if there is severe postprandial hyperglycaemia, though this combination has a lower efficacy on HbA1c than the other combinations).

The choice of combination must take into account the safety and contraindications of each drug class, the subject's age, the risk and degree of hypoglycaemia and the specific clinical and biochemical profile of each patient (Professional agreement).

These recommendations do not include two oral blood glucose lowering drugs that have been granted marketing authorisation since 2006: exenatide, an incretin mimetic (MA November 2006), sitagliptin, a dipeptidylpeptidase-4 inhibitor (MA March 2007) and vildagliptin (MA September 2007).
The different stages of treatment are summarised in the table below.

Therapeutic strategy (LTC 8 - Type 2 Diabetes)[30]

HbA1c levels	Treatment	Target HbA1c
HbA1c between 6 % and 6.5 % despite DLC	Metformin monotherapy (or AGI in the case of intolerance or contraindication)	< 6.5%
HbA1c > 6.5 % despite DLC	Metformin monotherapy or Insulin secretor or AGI	Maintain HbA1c < 6.5 %
HbA1c > 6.5% despite monotherapy and DLC	Dual oral therapy	Reduce HbA1c < 6.5 %
HbA1c > 7% despite dual oral therapy and DLC	Triple oral therapy: metformin + insulin secretor + glitazone or - insulin + metformin ± other OAD except glitazone	Reduce HbA1c < 7 %
HbA1c > 8 % despite triple oral therapy and DLC	Insulin + metformin ± other OAD except glitazone	Reduce HbA1c < 7 %

DLC: diet and lifestyle counselling; OAD: oral antidiabetics; AGI: intestinal alphaglucosidase inhibitors

30 Management of diabetes: Type 2 diabetes. Doctor's Guide - Long-term Conditions, HAS - May 2006.

Role of GALVUS:
The Committee notes that in combination with metformin, two non-inferiority studies versus an active comparator (glimepiride and pioglitazone at the non-optimal dose of 30 mg/day) are available.
As the Committee does not have access to any other direct comparison versus other dual therapies, it cannot provide a verdict on this combination in comparison with the recommended dual therapies. In addition, there are alternative treatments.
GALVUS should primarily be used in combination with metformin when diet, exercise and metformin do not adequately control glycaemia.

The Committee wishes to emphasise that the combination of sulfonylurea and vildagliptin has a limited role, if metformin is contraindicated or poorly tolerated. Hepatic impairment, heart failure and moderate to severe renal impairment, in which vildagliptin is not recommended, are also contraindications for metformin. The combination of sulfonylurea + vildagliptin therefore only involves patients who are intolerant to metformin, which is difficult to evaluate in practice and is poorly documented.

Given the limited role of glitazone monotherapy, the Committee considers that the role of the glitazone + vildagliptin combination is very limited. In addition, as the contraindications of metformin and vildagliptin are very similar, the combination of glitazone + vildagliptin would only be useful for those patients who are intolerant to metformin.

GALVUS is not recommended in patients with moderate to severe renal insufficiency or heart failure (NYHA class III or IV) and must not be used in patients with hepatic impairment, including patients with pre-treatment ALT or AST levels of more than 3 times the ULN.

4.4. Target Population
According to the indication in the marketing authorisation, the target population for GALVUS consists of patients with type 2 diabetes treated:
- with metformin when diet, exercise and metformin do not adequately control glycaemia;
- with a sulfonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulfonylurea and for whom metformin is inappropriate due to contraindications or intolerance;
- with a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate.

Data from the study conducted using the permanent Sample of Members of National Insurance Scheme (EPAS) established by the National Salaried Workers' Health Insurance Fund (CNAMTS)[31] indicate that the prevalence of diabetes treated in Metropolitan France for all social security regimes was 3.8% in 2005, and that the mean annual increase observed between 2000 and 2005 was 5.7%. On the basis of these percentages and assuming that the mean annual increase noted between 2000 and 2005 was the same as between 2005 and 2006, and that this remained constant in 2006 and 2007, the number of patients treated for diabetes in 2007 would be approximately 2,485,000 patients[32].
91% of these patients are type 2 diabetics (ENTRED 2001-2003 – diabetes network N°29 – September 2006).

According to the partially published results of the ECODIA 2 study (Diabetes networks N°31 – March 2007): 83.2% of patients with type 2 diabetes are treated with oral blood glucose lowering drugs without insulin, of whom 24% are treated with metformin monotherapy, 21.6% with a sulfonylurea monotherapy and 1.5% with a glitazone monotherapy.
The ECODIA 2 study data indicate that 68% of patients have HbA1c levels above 6.5%.

31 Diabète traité, quelles évolutions entre 2000 et 2005 [Treated diabetes: changes between 2000 and 2005], Prat Organ Soins 2007 ; 38 (1) :1-12
32 based on the population as defined by INSEE on 1 January 2008.

The percentage of patients in whom there is a contraindication or intolerance to metformin is not well understood. The hypothesis has been put forward that 20% of patients are affected by this.

The population of patients for whom a properly administered metformin monotherapy has failed would therefore appear to be 307,000 people, the population of those for whom properly administered sulfonylurea monotherapy has failed and for whom metformin is not appropriate because of contraindication or intolerance would be 55,300, and the population of patients for whom properly administered glitazone monotherapy has failed would be 19,200 people, giving a total of 381,500 people affected by the indications in the marketing authorisation.

The Committee repeats that GALVUS is not recommended in patients with moderate to severe renal insufficiency or heart failure (NYHA class III or IV) and that this product must not be used in patients with hepatic impairment, including patients with pre-treatment ALT or AST levels of more than 3 times the ULN.
These conditions are also contraindications to metformin, but it is difficult to count how many patients are affected.

As a result, the population given above is a high estimate of the population given in the marketing authorisation.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance (boxes of 30 and 60 tablets) and on the list of medicines approved for use by hospitals and various public services(boxes of 30, 60 and 90 tablets) for the indications and at the dosages given in the marketing authorisation.

The Transparency Committee is asking for a study to be done on a representative sample of French patients with type 2 diabetes who have been treated with GALVUS. This study would aim to describe the actual treatment situation:L

- characteristics of treated patients (including age, HbA1c level before treatment, renal, hepatic and cardiac function);
- conditions in which this product is used (indication, dosage, concomitant treatments etc);
- treatment maintenance rate;
- how many patients stop treatment and for what reasons;
- changes in HbA1c and weight, and occurrence of hypoglycaemia, over the long term (2 years).

The study duration, to be determined by a scientific committee, must be justified, and must be long enough to meet the Transparency Committee's requirements.

If planned or current studies, particularly under the European Risk Management Plan, do not answer all the questions posed by the Transparency Committee, a specific study will have to be carried out.

4.5.1 Packaging: these are appropriate for the prescription conditions

4.5.2 Reimbursement rate: 65%