

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

21 November 2012

GALVUS 50 mg, tablets

B/30 (CIP code: 34009 381 951 6 3)

B/60 (CIP code: 34009 383 221 5 6)

B/90 (CIP code: 34009 571 465 5 9)

Applicant: NOVARTIS PHARMA S.A.S.

INN	vildagliptin
ATC Code (2012):	A10BH02 (DPP-4 inhibitor or gliptin)
Reason for the review:	Extension of indication
Lists concerned	National Health Insurance (CSS L.162-17) for boxes of 30 and 60 tablets Hospital use (CSP L.5123-2) for all 3 packagings
Indication concerned	"Vildagliptin is indicated in the treatment of type 2 diabetes as monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance."

Transparency Committee votes:

AB	<u>Insufficient</u> for reimbursement by the National Health Insurance as monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.
IAB	Not applicable
Therapeutic use	Not applicable
Recommendations	<u>The Committee does not recommend inclusion</u> of GALVUS on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for use by hospitals in the extension of indication to <i>“monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance”</i>

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (centralised procedure): 26 September 2007 Date of extension of indication: 30 January 2012
Prescription and dispensing conditions/special status	List I

ATC Classification	2012	
	A	Alimentary tract and metabolism
	A10	Drugs used in diabetes
	A10B	Blood glucose lowering drugs, excluding insulins
	A10BH	dipeptidylpeptidase-4 (DPP-4) inhibitors
	A10BH02	vildagliptin

02 BACKGROUND

This is an application for registration for a new indication in the treatment of type 2 diabetes for the proprietary product GALVUS, as monotherapy.

Vildagliptin obtained European Marketing Authorisation on 26 September 2007 for the treatment of type 2 diabetes as dual oral therapy in combination with metformin or a sulphonylurea. In its opinion on 10 December 2008, the Committee granted:

- "a moderate efficacy/adverse s ratio in view of the quantitative effect seen on the reduction in HbA1c, uncertainties about liver safety and a safety profile, particularly in terms of cutaneous and cardiac profile, which is not well defined in view of the relatively non-serious characteristics in patients studied and the results of the studies available.
- a substantial AB in view of the results of available studies in terms of efficacy and safety.
- an IAB V for the treatment of type 2 diabetic patients."

As part of this application for an extension of indication, the company submitted five pivotal studies in particular. These studies had been submitted to the CHMP at the time of the initial Marketing Authorisation application for vildagliptin in 2007. At the time, the CHMP refused to grant Marketing Authorisation as monotherapy and requested that additional studies be conducted, particularly in patients with renal impairment and with heart failure.

Marketing Authorisation as monotherapy after lifestyle and dietetic measures have failed, or if metformin is contraindicated or not tolerated, was granted in January 2012 based on five pivotal studies previously submitted to CHMP and a safety study conducted in type 2 diabetic patients with renal impairment.

03 THERAPEUTIC INDICATIONS

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

As monotherapy:

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

As dual oral therapy in combination with:

- metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin,*
- a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to intolerance or contraindication,*
- a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate.*” (This indication cannot be evaluated by the TC as glitazones are no longer available in France)

**Indication already evaluated by the TC (cf opinion of 10 December 2008)*

04 DOSAGE IN THE NEW INDICATION

Adults

As monotherapy, the recommended daily dose of vildagliptin is 100 mg, administered as one dose of 50 mg in the morning and 50 mg in the evening.
Doses higher than 100 mg are not recommended.

The safety and efficacy of vildagliptin as triple oral therapy in combination with metformin and a sulphonylurea have not been established.

GALVUS can be administered with or without a meal (see also section 5.2 of the SPC).

Additional information in specific populations

Renal impairment

No dose adjustment is required in patients with mild renal impairment (creatinine clearance ≥ 50 ml/min). In patients with moderate or severe renal impairment or with end-stage renal disease (ESRD), the recommended dose of GALVUS is 50 mg once daily (see also sections 4.4, 5.1 and 5.2 of the SPC).

Hepatic impairment

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

Elderly (≥ 65 years)

No dose adjustments are necessary in elderly patients (see also sections 5.1 and 5.2 of the SPC).

Paediatric population (under 18 years old)

GALVUS should not be used in children and adolescents due to a lack of data on safety and efficacy (see also section 5.1).”

05 THERAPEUTIC NEED

Type 2 diabetes is a chronic progressive disease associated with high morbidity and mortality due to the micro- and macrovascular complications it causes. Chronic hyperglycaemia is the key pathogenic factor in the microvascular complications (retinopathy, nephropathy and neuropathy) and one of the contributors to macrovascular risk (coronary artery disease, lower limb arterial disease).

The objectives of therapeutic management are glycaemic control (control of HbA1c) and control of co-existing risk factors.

The choice of medical treatment and treatment goals must be tailored to individual patients (age, time since diagnosis of the diabetes, specific situations, risk of hypoglycaemia, etc.).

Type 2 diabetic patients are treated initially with lifestyle and dietary measures which must be continued at all stages.

Combating a sedentary lifestyle and dietary planning are essential interventions at all stages in the management of this disease.

Antidiabetic agents are used when lifestyle and dietary measures are no longer sufficient to control the diabetes.

The last updates of the international recommendations describe strategies following on from the results of the major trials (VADT, ACCORD, ADVANCE and the 10-year follow-up UKPDS results) and the availability of the incretin mimetic medicines.

In particular, the NICE guidelines¹ classify the existing DPP-4 inhibitors as dual therapy or as triple therapy. They also suggest that treatment with new medicines may only be continued if a significant fall in HbA1c is achieved at 6 months: -0.5% for the DPP-4 inhibitors, or -1% for exenatide (a GLP1 analogue).

The latest ADA/EASD guidelines² also propose changing the target HbA1c (7% to reduce microvascular risk). These guidelines, updated in 2012³ together with the SIGN guidelines (Scottish Intercollegiate Guidelines Network),⁴ now propose a patient-centred approach with individualised glycaemic targets. They provide a decision-making guide enabling the practitioner to adjust treatment for the patient's situation.

¹ National Institute for Clinical Excellence. London: NICE; 2009. Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes. This short clinical guideline partially updates NICE clinical guideline 66. The recommendations have been combined with unchanged recommendations from CG66 in NICE clinical guideline 87. <http://www.nice.org.uk/cg87>

² Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, *et al*. Medical management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 2009; 52 (1): 17-30.

³ Inzucchi S *et al*. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012 Jun; 35 (6): 1364-79

⁴ Scottish Intercollegiate Guidelines Network SIGN; 2010, Management of diabetes. A national clinical guideline. <http://www.sign.ac.uk/pdf/sign116.pdf>

In monotherapy, the reference first-line treatment is metformin.

In the case of metformin intolerance (mostly gastrointestinal) or contraindication (particularly in renal impairment), sulphonylureas are recommended.

The alpha-glucosidase inhibitors (acarbose and miglitol) and repaglinide are treatments used in monotherapy in the case of metformin or sulphonylurea contraindication or intolerance.

Metformin is contraindicated in renal impairment if the glomerular clearance is < 60 ml/min and sulphonylureas or insulin are primarily recommended in moderate renal impairment (clearance between 30 and 50 ml/min). Only insulin and repaglinide are recommended in severe renal impairment (clearance < 30 ml/min).

Sitagliptin (JANUVIA/XELEVIA) 100 mg and linagliptin (TRAJENTA) do not have a role in the treatment strategy for type 2 diabetic patients as monotherapy in patients who are inadequately controlled by diet and exercise if metformin is contraindicated or not tolerated in light of the available data. At the time of its evaluation the Committee only had studies with many methodological limitations (particularly modest efficacy, lack of superiority studies against active comparators, short-term studies, small number of patients evaluated, failure to include patients with a past history of cardiovascular disease, low patient responder rates) leading it to attribute an inadequate AB for reimbursement of these proprietary medicinal products by National Health Insurance (cf TRAJENTA opinion of 20 June 2012 and JANUVIA/XELEVIA 100 mg opinion of 18 July 2012).

In its opinion of 19 September 2012 on the registration of the proprietary medicinal products JANUVIA/XELEVIA containing 25 mg and 50 mg, the Committee deemed that:

- sitagliptin 50 mg can be offered to type 2 diabetic patients with moderate renal impairment (RI) particularly if sulphonylureas are contraindicated and before starting insulin in view of the results of the non-inferiority study against glipizide and the limited number of alternative treatments.
- Despite the low level of evidence from the data available but in view of the limited number of alternative treatments, sitagliptin 25 mg can be offered to type 2 diabetic patients with severe or end stage renal disease before starting insulin.

If correctly administered monotherapy with treatments which have been shown to be effective fails, a switch to dual therapy can be considered.

06 CLINICALLY RELEVANT COMPARATORS

The clinically relevant comparators for the medicinal product assessed are medicinal products which are available at the same stage of the treatment strategy and intended for the same population on the date of the evaluation.

In this case these are medicinal products indicated as second-line monotherapy in type 2 diabetic patients who are inadequately controlled by diet or exercise and for whom metformin is contraindicated or not tolerated.

06.1 Medicinal products

INN	Identical pharmacotherapeutic class	Name (Company)	Date of opinion	AB	IAB (Wording)	Reimbursement
Insulin secretagogues						
Sulphonylureas and their generics	No			Substantial		Yes
Alpha-glucosidase inhibitors (acarbose, miglitol)	No	GLUCOR (Bayer Santé) DIASTABOL (Sanofi Aventis)	5 September 2012 (renewal of registration)	Substantial		Yes
repaglinide	No	NOVONORM (Novo Nordisk)	21 July 2010 (renewal of registration)	Substantial		Yes
Gliptins						
sitagliptin	Yes	JANUVIA 100 mg/ XELEVIA 100 mg (MSD, Pierre Fabre)	18 July 2012 (extension of indication)	Insufficient for the 100 mg dosage	Not applicable	
sitagliptin	Yes	JANUVIA / XELEVIA 25 mg and 50 mg ⁵ (MSD, Pierre Fabre)	19 September 2012 (registration)	Low for the 25 mg and 50 mg dosages	IAB V	
linagliptin	Yes	TRAJENTA (Boehringer Ingelheim)	20 June 2012 (registration)	insufficient		

06.2 Other health technologies

Not applicable

► **Conclusion:** the most relevant of the comparators cited are the sulphonylureas (cf section 05. Therapeutic need)

⁵ JANUVIA 25 mg and JANUVIA 50 mg are two new dosages intended for dosage adjustment in type 2 diabetic patients with moderate to severe renal impairment or end stage renal disease.

07 INTERNATIONAL INFORMATION ABOUT THE MEDICINE

Country	REIMBURSEMENT	
	YES/NO If no, why	Population(s) Marketing Authorisation or restricted population
Germany, Denmark, Greece, Spain, Netherlands, Sweden, United Kingdom	YES	In the indications as listed in the European Marketing Authorisation
Italy	Evaluation in process	
Norway, Slovakia, Czech Republic	No - no file has been submitted	
United States	No – application withdrawn by the company from the FDA	

08 ANALYSIS OF AVAILABLE DATA

In support of its application the laboratory submitted the following data:

➤ Five pivotal studies:

- double-blind, randomised, placebo-controlled studies 2301⁶ and 2384,⁷ the objective of which was to evaluate the efficacy and safety of vildagliptin administered at doses of 50 mg once/day, 50 mg twice/day and 100 mg once/day as monotherapy to patients who were inadequately controlled by diet and exercise alone. *These studies have not been included as the dosages are outside of the Marketing Authorisation, they were conducted in one area of the Marketing Authorisation indication, patients receiving the 50 mg/day dosage (patients with renal impairment) were not included, no adjustment was made for secondary endpoints and because the multiple comparisons of the subgroup analyses were not performed and the comparator is not relevant.*
- double-blind, randomised study 2309⁸ and its 2-year extension phase,⁹ the objective of which was to evaluate the efficacy and safety of vildagliptin at a dosage of 50 mg twice daily compared to metformin administered as 2 g/day monotherapy on a non-inferiority basis over a period of 52 weeks: *this study cannot be included as it is outside of the Marketing Authorisation. For informational purposes, at 52 weeks, vildagliptin was not shown to be non-inferior to metformin in reducing HbA1c levels.*
- non-inferiority study 2327 against rosiglitazone and its extension phase. *These studies cannot be included by the Committee as the proprietary products containing rosiglitazone are no longer marketed in France.*
- double-blind, randomised study 2310,¹⁰ the objective of which was to demonstrate non-inferiority of vildagliptin monotherapy to a sulphonylurea monotherapy (gliclazide) in type 2 diabetic patients who were inadequately controlled by diet and exercise alone after treatment for 104 weeks. *This is the only study which can be included by the Committee*

⁶ Dejager S., Razac S., Foley J.E., Schweizer A. Vildagliptin in drug-naive patients with type 2 diabetes: a 24-week, double-blind, randomized, placebo-controlled, multiple-dose study. *Horm Metab Res* 2007; 39: 218-223.

⁷ Pi-Sunyer F.X., Schweizer A., Mills D., Dejager S. Efficacy and tolerability of vildagliptin monotherapy in drug-naive patients with type 2 diabetes. *Diabetes Res Clin Pract* 2007; 76: 132-138.

⁸ Schweizer A., Couturier A., Foley J.E., Dejager S. Comparison between vildagliptin and metformin to sustain reductions in HbA(1c) over 1 year in drug-naive patients with Type 2 diabetes. *Diabet Med* 2007; 24: 955-961.

⁹ Goke B., Hershon K., Kerr D. et al. Efficacy and safety of vildagliptin monotherapy during 2-year treatment of drug-naive patients with type 2 diabetes: comparison with metformin. *Horm Metab Res* 2008; 40: 892-895.

¹⁰ Foley J.E., Sreenan S. Efficacy and safety comparison between the DPP-4 inhibitor vildagliptin and the sulphonylurea gliclazide after two years of monotherapy in drug-naive patients with type 2 diabetes. *Horm Metab Res* 2009; 41: 905-909.

- Bibliographic data:
 - a non-inferiority study against acarbose¹¹ monotherapy in patients naive of any previous treatment was not included as it was outside of the Marketing Authorisation indication. Acarbose is used in monotherapy in metformin and sulphonylurea intolerance or contraindications but not as monotherapy from the outset.
 - two grouped analyses^{12,13} of data assessing vildagliptin in its different Marketing Authorisation indications cannot be included by the Committee as these were not indications which are being evaluated.
 - a placebo-controlled study^{14,15} and its extension phase which evaluated vildagliptin monotherapy at a dosage of 50 mg/day. This dosage is intended for patients with renal impairment (RI), although no patients with RI were included in this study. *This cannot therefore be included by the Committee.*

- Safety data
 - a study¹⁶ against metformin carried out in patients over 75 years old. This study cannot be included as the dosage of 100 mg once daily was outside of the Marketing Authorisation.
 - one study (23137) carried out in renal impairment¹⁷ leading to the Marketing Authorisation removing the precautions for use in renal impairment.
 - data from the last PSUR.
 - specific cardiovascular data.

08.1 Efficacy

8.1.1 Study 2310

Objective and methodology: this was a double blind, randomised, phase III monotherapy study, the objective of which was to demonstrate non-inferiority of vildagliptin to gliclazide in type 2 diabetic patients who were inadequately controlled by diet and exercise alone after treatment for 104 weeks.

Inclusion criteria:

Type 2 diabetic patients of at least 18 years old who were inadequately controlled (HbA1c level $\geq 7.5\%$ and $\leq 11\%$) by diet and exercise with a body mass index (BMI) between 22 and 45 kg/m² who had not taken antidiabetic treatment for at least 3 months or who had not previously been treated for more than 3 consecutive months.

¹¹ Pan C., Yang W., Barona J.P. et al. Comparison of vildagliptin and acarbose monotherapy in patients with Type 2 diabetes: a 24-week, double-blind, randomized trial. *Diabet Med* 2008; 25: 435-441.

¹² Pratley R.E., Rosenstock J., Pi-Sunyer F.X. et al. Management of type 2 diabetes in treatment-naive elderly patients: benefits and risks of vildagliptin monotherapy. *Diabetes Care* 2007; 30: 3017-3022.

¹³ Schweizer A., Dejager S., Foley J.E., Shao Q., Kothny W. Clinical experience with vildagliptin in the management of type 2 diabetes in a patient population ≥ 75 years: a pooled analysis from a database of clinical trials. *Diabetes Obes Metab* 2011; 13: 55-64.

¹⁴ Scherbaum W.A., Schweizer A., Mari A. et al. Efficacy and tolerability of vildagliptin in drug-naive patients with type 2 diabetes and mild hyperglycaemia*. *Diabetes Obes Metab* 2008 Feb; 10: 675-682.

¹⁵ Scherbaum W.A., Schweizer A., Mari A. et al. Evidence that vildagliptin attenuates deterioration of glycaemic control during 2-year treatment of patients with type 2 diabetes and mild hyperglycaemia. *Diabetes Obes Metab* 2008 Feb; 10: 1114-1124.

¹⁶ Schweizer A., Dejager S., Bosi E. Comparison of vildagliptin and metformin monotherapy in elderly patients with type 2 diabetes: a 24-week, double-blind, randomized trial. *Diabetes Obes Metab* 2009 Feb; 11: 804-812.

¹⁷ Lukashevich V., Schweizer A., Shao Q., Groop P.H., Kothny W. Safety and efficacy of vildagliptin versus placebo in patients with type 2 diabetes and moderate or severe renal impairment: A prospective 24-week randomized placebo-controlled trial. *Diabetes Obes Metab* 2011.

Main non-inclusion criteria:

- known cardiovascular disease (torsade de pointe, ventricular tachycardia, ventricular fibrillation, myocardial infarction or unstable angina), or treatment with angioplasty in the previous 3 months.
- recent signs or worsening of heart failure in the 3 months before inclusion,
- stroke event in the previous 6 months.

Administration regimen:

1092 patients were randomised to receive:

- either vildagliptin, dosage 50 mg twice daily (n = 456)
- or gliclazide (n = 456) initial dosage 80 mg/day which could be increased up to 320 mg/day following the regimen in the SmPC: 160 mg/day after treatment for 4 weeks, 240 mg/day after 8 weeks, 320 mg/day after 12 weeks.

Patients with inadequate glycaemic control after treatment for 24 weeks could also be given metformin.

Primary endpoint:

Mean change in HbA1c after 104 weeks of treatment compared to baseline.

Vildagliptin was deemed to be non-inferior to gliclazide if the upper limit of the 95% confidence interval of the difference in the change in HbA1c level between the two treatments (vildagliptin – gliclazide) was less than 0.3%.¹⁸

The protocol planned for the inclusion of 371 patients per treatment group for the *per protocol* analysis and a superiority analysis was planned for this endpoint if non-inferiority was established.

Secondary endpoint after treatment for 104 weeks:

- mean change in fasting blood glucose
- change in weight
- percentage of patients with HbA1c level <6.5%

Subgroup analyses stipulated in the protocol were carried out by age, BMI and HbA1c at inclusion. No adjustment method was used for the multiple comparisons and it is not possible to exclude an overestimation of the effect. As a result, no conclusions may be drawn from these exploratory analyses, which are not presented.

Results:

The patient characteristics at inclusion were similar in both treatment groups.

Mean patient age was 54.8 years old and the majority was obese (mean BMI 30.67 ± 5.25 kg/m²).

The diabetes had been present for an average of 2 years.

Mean HbA1c level at inclusion was 8.6% and almost 65% of patients had an HbA1c level of over 8%. The mean level was 8.4%.

After treatment for 2 years the patients treated with the gliclazide were taking an average dose of 209 mg. 44% of patients in the gliclazide group were receiving the maximum permitted dose of 320 mg/day and 16.7% were receiving 240 mg/day.

¹⁸ Vildagliptin and gliclazide were used at the optimal dosage recommended in their Marketing Authorisation. The SPC states however that the dosage ranges from 1 to 3 tablets per day and very occasionally 4 in gliclazide maintenance therapy.

The non-inferiority threshold chosen is more restrictive than is usually used in assessing antidiabetic agents (i.e. 0.4%)

Table 1: characteristics of patients included (randomised population)

	Vildagliptin group N = 546	Gliclazide group N = 546
Age		
Mean (years old)	55.2	54.2
<65 years old n (%)	426 (78.0)	445 (81.5)
≥75 years old n (%)	16 (2.9)	8 (1.5)
Mean weight (kg)	84.2	84.3
Body mass index (kg/m²)	30.5	30.8
< 30 kg/m ²	270 (49.5)	273 (50.0)
≥ 30 kg/m ²	276 (50.5)	272 (49.8)
≥ 35 kg/m ²	105 (19.2)	120 (22.0)
Mean HbA1c level (%)	8.60±1.04	8.69±1.07
Median HbA1c level (%)	8.4	8.5
Number (%) of patients with HbA1c at inclusion		
≤8%	194 (35.5)	181 (33.2)
>8%	352 (64.5)	365 (66.8)
≤9%	381 (69.8)	360 (65.9)
>9%	165 (30.2)	186 (34.1)
Mean fasting blood glucose (mmol/L)	10.78	10.81
Average duration of diabete (years)	2.43	1.86

Primary endpoint:

Table 2: change in HbA1c at 104 weeks in the per protocol population:

Treatment group	N	Mean baseline HbA1c (SD)	Mean change (SD) at week 104 compared to baseline.
vildagliptin	409	8.53 (0.05)	-0.47 (0.08)
gliclazide	409	8.70 (0.05)	-0.61 (0.08)
Estimated difference vildagliptin versus gliclazide			Difference between means (95% CI): 0.13 [-0.06; 0.33]

The difference between vildagliptin and gliclazide in terms of the fall in HbA1c after 104 weeks of treatment in the *per protocol* population was 0.13% 95%CI [-0.06; 0.33]. The upper limit of the confidence interval of this difference was above the threshold set (0.3%) and vildagliptin was therefore not shown to be non-inferior to gliclazide. This result was also found in the ITT population.

Approximately 75% of patients in each group completed the study.

The fall in HbA1c was greatest on vildagliptin and on gliclazide up to 32 weeks of treatment. Beyond that, HbA1c levels rose.

Secondary endpoints:

As non-inferiority was not established for the primary efficacy endpoint and the results based on these criteria cannot be used by the Committee. They are provided for information purposes.

- mean change in fasting blood glucose:

Vildagliptin was not shown to be non-inferior to gliclazide after treatment for 104 weeks.

- change in weight:

After treatment for 104 weeks, weight in the *per protocol* population increased by 0.75 ± 0.24 kg in the vildagliptin group and by 1.60 ± 0.23 kg in the gliclazide group, i.e. a difference of -0.85 kg; 95%CI [-1.42; -0.27]; *p* = 0.004).

- percentage of patients with HbA1c < 6.5%

The treatment goal was achieved by 14.2% of patients on vildagliptin (58/409) and by 15.2% of patients on gliclazide (62/407) in the per protocol population.

Rescue therapy with metformin at the average dose of 1500 mg/day was given to 29.7% of patients on vildagliptin (162/546) and to 20.7% of patients on gliclazide (113/546).

08.2 Safety/Adverse effects

8.2.1 Data from study 2310

At least one adverse event occurred in 69.5% of patients on vildagliptin (379/545) and in 73% of patients on gliclazide (398/545). These events were related to treatment in 12.1% of patients on vildagliptin (i.e. 66 patients) and in 18.5% of patients on gliclazide (101 patients).

The main adverse events were:

- infections (mostly rhinopharyngitis and influenza) in 37.1% of patients on vildagliptin and 38% of patients on gliclazide
- gastrointestinal disorders, mostly diarrhoea, in approximately 20% of patients (129 on vildagliptin and 113 on gliclazide)
- metabolic and nutritional disorders in 12.1% of patients in the vildagliptin group and in 10.8% of patients on gliclazide
- nervous system disorders, mostly headaches in 14.8% of patients on vildagliptin and in 12.7% of patients on gliclazide
- musculoskeletal and connective tissue disorders in approximately 25% of patients (138 on vildagliptin, 135 on gliclazide)
- vascular disorders in 9.5% of patients on vildagliptin, 11.2% of patients on gliclazide
- skin disorders in 10.8% of patients on vildagliptin, 14.3% of patients on gliclazide.

Hypoglycaemia was reported in four patients on vildagliptin (none had more than one episode of hypoglycaemia) and by fourteen patients on gliclazide (two of whom had at least two episodes of hypoglycaemia).

Treatment was stopped for adverse events in 32 patients in the vildagliptin group and in 35 in the gliclazide group.

A myocardial infarction occurred in seven patients on vildagliptin and in two on gliclazide. There were four cases of unstable angina in the gliclazide group and two in the vildagliptin group. There were 3 cases of ischaemic stroke on vildagliptin and none on gliclazide. There were four cases of heart failure in the gliclazide group and none in the vildagliptin group.

A total of 20 cardiac and cerebrovascular events were confirmed by the independent adjudication committee in the vildagliptin group (3.7%) and 26 (4.8%) in the gliclazide group.

8.2.2 Data from study 23137 in renal impairment

Objective and methodology: this was a randomised (2 to 1) double-blind, placebo-controlled, phase III study, the objective of which was to evaluate the safety of vildagliptin at a dosage of 50 mg/day as monotherapy or in combination with the antidiabetic treatment being taken previously in 525 type 2 diabetic patients who were inadequately controlled, with moderate (n = 294) or severe (n = 221) renal impairment, after treatment for 24 weeks.

The protocol planned for stratified randomisation particularly by grade of severity of the renal impairment.

The efficacy criteria (change in HbA1c, responder rates) were exploratory criteria.

Inclusion criteria:

Type 2 diabetic patients, aged over 18 years old, who were inadequately controlled (HbA1c $\geq 6.5\%$ and $\leq 10\%$) and had not been taking any antidiabetic treatment for at least 8 weeks or whose treatment had been stable for at least 4 weeks, particularly with sulphonylurea, glinide, α -glucosidase inhibitor or insulin, either alone or in combination.

Patients with a past cardiovascular history (myocardial infarction, unstable angina, stroke) in the previous 6 months were not included.

Administration regimen:

Five hundred and twenty-five (525) patients were randomised to receive the following treatment in addition to their prior antidiabetic treatment (if previously treated) or as monotherapy (if not treated):

- either vildagliptin, at a dosage of 50 mg/day (n = 165 in the group with moderate RI, n = 124 in the group with severe RI)
- or a placebo (n = 129 in the group with moderate RI, n = 97 in the group with severe RI).

Results:

The patient characteristics were similar at inclusion in both treatment groups.

The average age of patients in the moderate RI group was 68.6 years old (more than 70% of patients were over 65 years old). The patients were obese and had been diabetic for an average of 15.1 years with an average HbA1c of 7.8%. More than 2/3 of them were being treated with insulin alone or in combination with oral antidiabetic agents.

The average age of patients in the severe RI group was 64.3 years old (more than 50.7% of patients were over 65 years old). The patients were obese and had been diabetic for an average of 18.1 years, with an average HbA1c of 7.7%. More than 3/4 of them were being treated with insulin alone or in combination with oral antidiabetic agents.

3.7% of patients in the moderate RI group were receiving monotherapy (6 on vildagliptin and 5 on placebo) and 2.7% of the patients with moderate RI (5 on vildagliptin and 1 on placebo).

Overall, 88% of patients included have completed the study.

Rescue therapy with rescue insulin (planned in the protocol if glycaemic control was inadequate, as an addition to the current treatment or as intensification) was given to 9 patients on vildagliptin and 13 on placebo in the moderate RI group and to 1 patient on vildagliptin and 3 on placebo in the severe RI group.

Adverse events occurred in 67.5% of patients in the moderate RI group (110/163) on vildagliptin and in 72.9% of patients (94/129) on placebo, and in 72.6% of patients (90/124) on vildagliptin and 74.2% of patients (72/97) on placebo in the severe RI group. The events were related to the treatment in 18.4% of patients on vildagliptin and 20.2% of patients on placebo in the moderate RI group and in 21% of patients on vildagliptin and 17.5% of patients on placebo in the severe RI group.

These events are summarised in the table below:

Table 3: main adverse events reported

Type of adverse events	Moderate RI n (%)		Severe RI N (%)	
	Vildagliptin group N = 163	Placebo group N = 129	Vildagliptin group N = 124	Placebo group N = 97
Infections	38 (23.3)	35 (27.1)	38 (30.6)	19 (19.6)
Nervous system disorders	37 (22.7)	30 (23.3)	28 (22.6)	16 (16.5)
Metabolic disorders	36 (22.1)	22 (17.1)	33 (26.6)	30 (30.9)
Hypoglycaemia	28 (17.2)	15 (11.6)	19 (15.3)	12 (12.4)
Severe hypoglycaemia	2 (1.2)	2 (1.6)	2 (1.6)	2 (2.1)
Skin disorders	27 (16.6)	17 (13.2)	28 (22.6)	23 (23.7)
Muscle disorders	25 (15.3)	20 (15.5)	9 (7.3)	14 (14.4)
Gastrointestinal disorders	22 (13.5)	20 (15.5)	27 (21.8)	24 (24.7)
Peripheral oedema	18 (11.0)	13 (10.1)	21 (16.9)	18 (18.6)
Cardiac adverse event	8 (4.9)	11 (8.5)	15 (12.1)	12 (12.4)

Four patients on vildagliptin and 7 on placebo stopped treatment because of adverse events in the moderate RI group, compared to 11 patients on vildagliptin and 6 patients on placebo in the severe RI group.

There was no particular signal for hepatic or cutaneous adverse events, oedema or pancreatitis. The most common adverse events were hypoglycaemia, infections (mostly rhinopharyngitis) and peripheral oedema.

In terms of cardiovascular safety, one case of syncope was reported in a patient with severe RI. Three hepatic events (AST/ALT > 5 ULN) were reported, in one patient with moderate RI on vildagliptin and in two on placebo.

8.2.3 SmPC data

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 Liver function tests normalisation, treatment with GALVUS should not be reinitiated.

Cardiac failure

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

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.

Pancreatitis

In post-marketing experience there have been spontaneously reported adverse reactions of acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis:

persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of vildagliptin. If pancreatitis is suspected, vildagliptin and other potentially suspect medicinal products should be discontinued.”

8.2.4 Data from the last PSUR (period from 1st March 2011 to 29 February 2012) in all of the indications for vildagliptin

The analysis of data from the last international GALVUS PSUR is consistent with the information about risk as it appears in the current Marketing Authorisation. Safety is monitored closely as part of the international risk management plan.

- Transaminase elevation and Drug-induced liver injury (DILI):

In 2011 the following phrase was added in section 4.8 to the existing wording about liver safety from clinical trial data: *Adverse effects* “Since the launch of the product, rare cases of hepatic dysfunction (including hepatitis) have been reported and liver function returned to normal after discontinuation of treatment: 47 liver events deemed to be unexpected (transaminases over 10 times normal, jaundice, hepatic impairment) have been seen including two deaths. Eleven of these 47 cases occurred in patients with a medical history of liver disease, one case had pancreatitis with jaundice and increased transaminases and another had heart failure with possible ischaemic hepatitis.

- Angioedema:

The PSUR analysis identified 121 cases including 17 cases of angioedema or Quincke's oedema confirmed by healthcare professional both with concomitant ACE inhibitor treatments and three cases of pharyngeal or lingual oedema which were not confirmed by a healthcare professional. The other 101 cases were moderate angioedema or pseudo angioedema in sites other than the pharynx or tongue or sites which were not specified, many of which were associated with concomitant ACE inhibitor treatment.

- Acute pancreatitis:

One hundred and twenty-four (124) potential cases were identified. Three of the 64 cases reporting pancreatitis or acute pancreatitis described acute necrotising pancreatitis, one of which was fatal. The 60 remaining cases were either isolated increases in lipase/amylase or transaminase.

- Skin lesions:

The variation was approved by the CHMP in May 2012 to add a post-marketing adverse effect of unknown frequency: bullous or exfoliative skin lesions. This followed a review of cases of skin lesions on vildagliptin requested by the CHMP. The PSUR identified 63 cases of urticaria, 3 cases of vasculitis, 4 cases of bullous pemphigoid and 4 other cases of erythema multiform, 4 cases of the Stevens Johnson syndrome/toxic epidermolysis including 2 cases received allopurinol, 23 cases of desquamating rash and 23 other cases of rash, 14 cases of stomatitis/buccal or oropharyngeal ulceration, 31 cases of bullous lesions and 1 case of skin ulceration.

- Serious infections:

Two hundred and ninety-six (296) of the 368 events deemed to be serious were confirmed by a healthcare professional. The most common infections were respiratory, gastrointestinal, urinary and sepsis. Half of the 62 deaths listed were due to respiratory infection.

- Reduced cardiac function:

One hundred and twenty-five (125) cases of heart failure were identified including 2 fatal cases, 27 cases of myocardial infarction including 3 deaths, 14 cases of cardiomyopathy, 3 cases of cardiogenic shock/reduced ejection fraction and 3 cases of valve disease, 2 cases of cardiopulmonary failure (including 1 death), 2 cases of dysrhythmia, 4 cases of unspecified cardiac disorders (including 1 death) and one sudden death.

- Muscle events/ myopathy with or without concurrent statin use :

Thirty-nine (39) cases of muscle damage or rhabdomyolysis were reported. Eighteen (18) of the 27 patients not treated with statins had conditions predisposing to muscle disorders (4 with fall and immobilisation, alcoholism, treatments which can cause rhabdomyolysis etc.), 5 cases were poorly documented to allow an evaluation and the remaining 4 cases had no concomitant treatment, intercurrent event/lifestyle factors or medical history to which this muscle event could be attributed.

- Hypoglycaemia:

Three hundred and twenty-eight (328) cases were identified, 2/3 of which were confirmed by a healthcare professional. Twenty nine (29) of these 328 cases met the RMP definition of severe hypoglycaemia (life-threatening or coma). The majority of cases had risk factors such as other concomitant antidiabetic treatment (insulin, sulphonylurea, etc.), a period of fasting or exercise, ingestion of alcohol, irregular meals or intercurrent infection/disease.

- Neuropsychiatric events (depression):

Ten (10) cases were reported including 8 with attempted suicide and suicidal ideation. Many of the patients had a medical history of depression or anti-depressant treatment and 2 cases were suicide.

8.2.5 Data from other literature sources in patients with heart failure and overall cardiovascular safety data

A combined analysis of all of the studies which evaluated vildagliptin (excluding the open studies), including 184 type 2 diabetic patients with known heart failure (HF) at inclusion, 131 of whom were treated with vildagliptin (70% at a dose of 50 mg twice daily) and 53 with comparator was submitted by the company.

Compared to the whole population the HF patients treated with vildagliptin were older (average age 64 years old compared to 56 years old in the comparator group) and had a slightly higher BMI (32.9 kg/m² compared to 31.4 kg/m²). Slightly more had mild renal impairment (approximately 50% compared to approximately 30% for the comparators). On the other hand, glycaemic control was similar (mean HbA1c 8.0% compared to 8.2%) as was the length of history of the diabetes (4.9 years compared to 4.2 years). These characteristics were similar for HF patients treated with a comparator.

The overall incidence of adverse events in HF patients was 60.4% on vildagliptin 50 mg twice daily, 62.3% on any comparator and 77.8% on a placebo. The highest incidences were found in the categories of “infections” (28.6% on vildagliptin 50 mg twice daily and 32.1% on comparators), “nervous system disorders” (23.1% and 20.8%), “gastro-intestinal disorders” (17.6% and 13.2%), “muscular and connective tissue disorders” (14.3% and 24.5%) and “cardiac disorders” (13.2% and 15.1%).

A meta-analysis¹⁹ which included 25 double-blind, placebo or active comparator controlled randomised phase III studies (14 monotherapy, 11 dual therapy), lasting an average of 12 weeks was designed to evaluate²⁰ the cardiovascular and cerebrovascular profile of vildagliptin. The meta-analysis included 13,570 patients (1393 on vildagliptin, 50 mg/day, 6116 patients on vildagliptin, 50 mg twice daily and 6061 patients on a placebo or active comparator) with an average age of 56 years old (20% were over 65 years old). The majority was obese (mean BMI 31.3 kg/m²), their mean HbA1c was 8.1% and most had cardiovascular risk factors. 60% of the patients analysed had hypertension, more than 40% had dyslipidaemia, more than 30% had renal

¹⁹ Schweizer A., Dejager S., Foley J.E., Couturier A., Ligueros-Saylan M., Kothny W. Assessing the cardio-cerebrovascular safety of vildagliptin: meta-analysis of adjudicated events from a large Phase III type 2 diabetes population. *Diabetes Obes Metab* 2010 Feb; 12: 485-494.

²⁰ prospectively by an independent adjudication committee

impairment, approximately 40% had two or more combined risk factors and 15% were deemed to be at high risk.²¹

The primary endpoint was development of a cardiovascular or cerebrovascular event, a composite endpoint defined by the following events: acute coronary syndromes, transient ischaemic events, confirmed by imaging, cerebrovascular events and cardiovascular deaths. The data were not searched exhaustively. Heterogeneity tests were not significant.

The relative risk of developing a cardiac or cerebrovascular event compared to placebo or active comparators was 0.88 95%CI [0.37; 2.11] in the group treated with vildagliptin, dose 50 mg/day and 0.84 95%CI [0.62; 1.14] in the group treated with vildagliptin, dose 50 mg twice daily.

The authors of the meta-analysis considered that vildagliptin was not associated with an increased risk of cardiovascular or cerebrovascular events.

08.3 Summary & discussion

Vildagliptin has been evaluated principally in two studies in its Marketing Authorisation monotherapy indication.

One double-blind, randomised, non-inferiority study compared vildagliptin to a sulphonylurea, gliclazide, as monotherapy for 104 weeks in 1092 type 2 diabetic patients who were inadequately controlled with diet and exercise alone.

Average patient age at inclusion was 54.8 years old and the majority was obese. The diabetes had been present for an average of 2 years. Mean HbA1c was 8.6%. HbA1c was over 8% in approximately 65% of patients.

The difference between vildagliptin and gliclazide in terms of the reduction in HbA1c (primary endpoint) after treatment for 104 weeks in the *per* protocol population was 0.13% 95%CI [-0.06; 0.33]. The upper limit of the confidence interval of this difference was above the cut-off set (0.3%), **and vildagliptin was not shown to be non-inferior to gliclazide**. The same result was found in the ITT population.

The main adverse events reported in the two groups were infections, gastrointestinal problems and musculoskeletal disorders. The small number of cases of hypoglycaemia (in 4 patients on vildagliptin and 14 on gliclazide) may be due to the gradual titration of gliclazide and cannot be analysed qualitatively.

Despite the debatable level of evidence, the number of responder patients was small. The treatment goal was achieved by approximately 15% of patients in each treatment group.

This study did not include patients in whom metformin was contraindicated or not tolerated and no data are therefore available in this target population for the wording of the Marketing Authorisation.

A double-blind 2:1 randomised study, stratified particularly according to grade of severity of the renal impairment compared vildagliptin 50 mg/day to placebo for 24 weeks in 525 type 2 diabetic patients who were inadequately controlled and were suffering from moderate (n = 294) or severe (n = 221) renal impairment. Vildagliptin or the placebo were taken as monotherapy or combined with another antidiabetic agent already being taken.

The primary objective was safety. The efficacy criteria (change in HbA1c, responder rate) were exploratory.

The average age of patients with moderate RI at inclusion was 68.6 years old. The patients were obese and had been diabetics for an average of 15.1 years with an average HbA1c of 7.8%. More

²¹ High risk defined by past cardiac or cerebrovascular history: heart failure, cerebrovascular ischaemia and/or thromboembolic events, cardiac ischaemia.

than 2/3 was being treated with insulin alone and/or in combination with oral antidiabetic agents. The average age of patients with severe RI at inclusion was 64.3 years. The patients were obese and had been diabetics for an average of 18.1 years with an average HbA1c of 7.7%. More than 3/4 was being treated with insulin alone and/or in combination with oral antidiabetic agents.

Adverse events were reported:

- in 67.5% of patients (110/163) on vildagliptin and in 72.9% of patients (94/129) on placebo in the moderate RI group
- in 72.6% of patients (90/124) on vildagliptin and 74.2% of patients (72/97) on placebo in the severe RI group.

These adverse events were related to treatment:

- in 18.4% of patients on vildagliptin and in 20.2% of patients on placebo in the moderate RI group,
- and in 21% of patients on vildagliptin and 17.5% of patients on placebo in the severe RI group.

The most common adverse events were hypoglycaemia, infections (mostly rhinopharyngitis) and peripheral oedema.

Four patients on vildagliptin and 7 on placebo stopped treatment because of adverse events in the moderate RI group, compared to 11 patients on vildagliptin and 6 patients on placebo in the severe RI group.

There was no particular signal for hepatic or cutaneous adverse events, oedema or pancreatitis.

There are no data from this study on:

- safety in patients with end stage renal disease
- safety compared to active comparators (particularly sulphonylureas and insulin)
- robust safety data for vildagliptin monotherapy (few patients included). Only 3.7% of patients with moderate RI (6 on vildagliptin and 5 on placebo) and 2.7% of patients with moderate RI (5 on vildagliptin and 1 on placebo) were receiving monotherapy.
- efficacy in diabetic patients with RI.

There is no superiority study against an active comparator.

There are no morbidity and mortality data and no study is ongoing.

In the 23 February 2012 version of the RMP, the 3 identified risks are: transaminase elevation and Drug-induced liver injury (DILI), angiooedema and acute pancreatitis.

The potential risks include: skin lesions, serious infections, compromised cardiac function, muscle events/myopathy with or without concurrent statin use, hypoglycaemia, neuropsychiatric events and breast cancer.

These risks are subject to close monitoring in the frame of the RMP and a specific safety monitoring study has been carried out by French pharmacovigilance.

The cardiovascular safety data are based on relatively small numbers.

08.4 Study Programme

In addition to conventional pharmacovigilance the European RMP includes:

- a long term observational study with the objective of comparing safety of use in 9,000 patients treated with GALVUS and 54,000 patients treated with other oral antidiabetic agents in the General Practice Research Database (GPRD) – *study ongoing, 1st interim report submitted to CHMP in 2010, end date not possible to estimate.*
- a usage study with the objective of describing the characteristics of patients who are treated and evaluating correct use of GALVUS. This is a study from databases which will be carried out in several European countries (Germany, Austria, Denmark, France, Great Britain and

Sweden). Approximately 500 patients will be included in each country. The study is completed and the study report which has been submitted to CHMP is being evaluated.

- two randomised, multi-centre, clinical studies to evaluate the safety of GALVUS (50 mg/ day) in patients with moderate and severe renal impairment treated initially with insulin or by a sulphonylurea: one will assess GALVUS against a placebo (in 450 patients in different European countries including France) and the other against sitagliptin (in 150 patients in the United States). These studies have been completed, the study reports have been submitted to the CHMP and they support the lifting of the restriction obtained in November 2011 for patients with moderate to severe renal impairment.
- a randomised multi-centre study to evaluate the safety of GALVUS (50 mg/ day) against a placebo in diabetic patients with heart failure, lasting 52 weeks. This study has been completed and the study report is due to be submitted to the CHMP in December 2012.

09 THERAPEUTIC USE

Not applicable (cf paragraph 010.1)

In view of all of the information and following the debate and vote, the Committee has come to the following conclusions:

010.1 Actual benefit

Type 2 diabetes is a chronic disease with potentially serious, particularly cardiovascular, complications.

GALVUS is used for the treatment of hyperglycaemia.

Vildagliptin has been evaluated in monotherapy after failure of diet and exercise. Its efficacy has not been established in this indication. Non-inferiority against gliclazide (the first-line reference monotherapy treatment when metformin is not tolerated or contraindicated) has not been demonstrated.

There are no efficacy data in the target patients for the Marketing Authorisation indication in whom metformin is not tolerated or contraindicated, particularly in renal impairment.

The safety study conducted in diabetic patients with renal impairment has not evaluated monotherapy robustly (few patients included, 17/525).

The efficacy data are limited and efficacy cannot be evaluated against active comparators, particularly the sulphonylureas. A study against active comparators such as metformin or sulphonylureas would allow the utility of this proprietary medicinal product to be evaluated as monotherapy, particularly as the reduction seen with the comparators, which have also been shown to have a positive impact in terms of morbidity and mortality,²² is substantial (in the region of -1 to -1.5%). There is no superiority study against an active comparator, particularly the sulphonylureas.

The benefit of vildagliptin monotherapy cannot therefore be assessed.

Since vildagliptin was put on the market, cases of adverse effects which were not identified in the clinical trials have been reported. These involve particularly cases of pancreatitis, skin reactions, serious infections, neuropsychiatric events and muscle disorders.

The long-term risks relating particularly to the occurrence of pancreatitis and allergic reactions are poorly understood and there are uncertainties and concerns about the safety profile, particularly as regards to the liver.

Risks are identified in the 23 February 2012 version of the RMP: transaminase elevation and liver disorders, angioedema and acute pancreatitis. The potential risks include in particular: reduced cardiac function and breast cancer.

For these reasons, the efficacy/adverse effects ratio of GALVUS monotherapy cannot be quantified.

In light of the available data, this proprietary medicinal product cannot be recommended as monotherapy. Alternative medicinal products are available for the treatment of diabetic patients (principally metformin and sulphonylureas). If metformin is contraindicated, the main medicinal products recommended are sulphonylureas and insulin in moderate renal impairment and insulin in severe renal impairment. Dual therapy can be considered if correct monotherapy with treatments which have been proven to be effective fails.

There are alternative medicines to this proprietary medicinal product.

²² Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998, 352, 854-65.

Public health benefit

The public health burden of type 2 diabetes is high. The burden from the sub-group of patients in whom GALVUS is indicated as monotherapy for second-line treatment (type 2 diabetic patients inadequately controlled by diet and physical exercise alone and for whom metformin is contraindicated or not tolerated) is moderate.

The improvement in the therapeutic management of type 2 diabetic patients is a public health need.

In light of the results of the non-inferiority study against a relevant comparator (gliclazide), GALVUS is not expected to have an impact on glycaemic control and therefore on the morbidity and mortality of patients treated compared with the other treatments available.

In addition there are uncertainties as to whether these results can be extrapolated to current practice as this study did not include any patients for whom metformin was contraindicated or poorly tolerated.

In the current state of knowledge, the proprietary medicinal product GALVUS does not meet the public health need.

As a result, GALVUS is not expected to offer a public health benefit.

As a result, the Committee considers that the actual benefit of GALVUS as monotherapy in patients whose glycaemic control is inadequate despite diet and physical exercise alone and for whom metformin is not tolerated or is contraindicated is insufficient for reimbursement by National Health Insurance.

010.2 Improvement in actual benefit (IAB)

Not applicable.

010.3 Target population

Not applicable.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee does not recommend inclusion of the proprietary medicinal product GALVUS on the list of medicines reimbursed by the National Health Insurance and on the list of medicines approved for hospital use in the extension of the indication to “*monotherapy in patients whose glycaemic control is inadequate despite dietary and exercise measures alone and for whom metformin is inappropriate because of intolerance or contraindications*”.