HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
29 October 2014

GALVUS 50 mg, tablet
B/30 (CIP: 34009 381 951 6 3)
B/60 (CIP: 34009 383 221 5 6)
B/90 (CIP: 34009 571 465 5 9)

JALRA 50 mg, tablet
B/30 (CIP: 34009 498 599 0 0)
B/60 (CIP: 34009 498 600 9 8)
B/90 (CIP: 34009 578 911 0 7)

Applicant: NOVARTIS PHARMA S.A.S.

INN	Vildagliptin
ATC Code (2013)	A10BH02 (Dipeptidyl peptidase 4 (DPP-4) inhibitors)
Reason for the review	**Extension of indication**
Lists concerned	B/30 and B/60: **National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2) B/90: **Hospital use** (French Public Health Code L.5123-2)
Indications concerned	"Vildagliptin is indicated in the treatment of type 2 diabetes mellitus in adults: **Vildagliptin is also indicated in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control."**

Actual Benefit	✓ **In combination with insulin alone: insufficient** ✓ **In combination with insulin and metformin: moderate**
Improvement in Actual Benefit	✓ **As dual therapy in combination with insulin:** Not applicable. ✓ **As triple therapy in combination with insulin and metformin:** In the absence of direct comparative data versus an active comparator, the Transparency Committee considers that GALVUS/JALRA does not provide any improvement in actual benefit (level V, non-existent) in the treatment of patients with type 2 diabetes in combination with insulin and metformin, in patients not achieving or maintaining the glycaemic targets on a combination of insulin + metformin.
Therapeutic Use	✓ **In combination with insulin alone:** Gliptins (including vildagliptin) have no role in therapeutic strategy for the management of type 2 diabetic patients as dual therapy in combination with insulin. ✓ **In combination with insulin and metformin:** As triple therapy, vildagliptin is a treatment option that can be added to the combination of insulin + metformin in patients who do not achieve or maintain glycaemia targets with a combination of insulin and metformin. This treatment situation (triple therapy of a gliptin in combination with insulin and metformin) is for patients who cannot be treated with a sulfonylurea.
Recommendations	**-**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised procedure)	Initial date (GALVUS): September26th 2007 Initial date (JALRA): November 19th 2008 Extension of indication (GALVUS): October 29th 2012 Extension of indication (JALRA): November 29th 2012 Risk management plan (RMP) + national monitoring
Prescribing and dispensing conditions/special status	List I

ATC Classification	2013	
	A	Alimentary tract and metabolism
	A10	Drugs used in diabetes
	A10B	Blood glucose lowering drugs, excl. insulins
	A10BH	Dipeptidyl peptidase 4 (DPP-4) inhibitors
	A10BH02	Vildagliptin

02 BACKGROUND

The GALVUS/JALRA proprietary medicinal products are included on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the treatment of type 2 diabetes as dual oral therapy in combination with either metformin or a sulfonylurea (in cases where metformin is not appropriate due to intolerance or contraindication), in patients whose glycaemic control is inadequate despite a maximum tolerated dose of metformin or sulfonylurea as monotherapy. GALVUS/JALRA is not refundable in its indication as monotherapy.[1]
Vildagliptin, active ingredient of GALVUS/JALRA, amplifies the incretin effect on the islets of Langerhan through potent and selective inhibition of dipeptidylpeptidase (DPP-4). Vildagliptin can be used in patients presenting moderate or severe renal impairment or end-stage renal disease (ESRD) (at adjusted dose).
This request concerns the use of vildagliptin **in combination with insulin, with or without metformin,** when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control. The extension of indication in combination with a sulfonylurea and metformin (triple oral therapy) is the subject of a separate opinion.

In a letter dated July 2nd 2013, the Transparency Committee informed all the companies using incretin-based drugs (gliptins and GLP-1 analogues) of its desire to re-assess the actual benefit, improvement in actual benefit and the target population of all the proprietary medicinal products concerned. In this context, the Committee suspended the ongoing assessment of all files, including the GALVUS/JALRA file.
The Committee office, in its meeting on March 12th 2014, decided not to re-assess the incretin-based drugs. In fact, in the current state of knowledge and of data available in the literature taken into account by the FDA, EMA and ANSM [French National Agency for Medicines and Health Products Safety], no evidence to date supports a link between the incretin-based drugs and the increased risk of pancreatitis and pancreatic cancer (which have in particular motivated the re-assessment) which nevertheless remain risks to be monitored.[2] These risks will be the subject of increased pharmacovigilance monitoring, in morbidity-mortality clinical studies and in epidemiological studies to which the Committee will remain attentive.

[1] Indication assessed by the Transparency Committee on 21/11/2012 (AB insufficient).
[2] Egan AG et al. Pancreatic safety of incretin-based drugs-FDA and EMA assessment. N Engl J Med 370;9. February 27, 2014.

03 THERAPEUTIC INDICATIONS

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

As monotherapy1
- 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[3]
- 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.[4]

As triple oral therapy in combination with[5]
- a sulfonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

Vildagliptin is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control."

04 DOSAGE

Adults
When used as monotherapy, in combination with metformin, in combination with thiazolidinedione, in combination with metformin and a sulfonylurea, or in combination with insulin (with or without metformin), the recommended daily dose of vildagliptin is 100 mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening.
When used in dual combination with a sulfonylurea, the recommended dose of vildagliptin is 50 mg once daily administered in the morning. In this patient population, vildagliptin 100 mg daily was no more effective than vildagliptin 50 mg once daily.
When used in combination with a sulfonylurea, a lower dose of the sulfonylurea may be considered to reduce the risk of hypoglycaemia.
…
Doses higher than 100 mg are not recommended.
…
Elderly (≥ 65 years)
No dose adjustments are necessary in elderly patients.
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/JALRA is 50 mg once daily

Hepatic impairment

[3] Indications assessed by the Transparency Committee on 10/12/2008 (AB substantial- IAB V)
[4] Indication obsolete because the thiazolidinediones have not been marketed in France since 2011.
[5] This indication is the subject of a separate opinion.

GALVUS/JALRA 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).

Paediatric population
GALVUS/JALRA is not recommended for use in children and adolescents (< 18 years). The safety and efficacy of GALVUS in children and adolescents (< 18 years) have not been established. No data are available.

05 THERAPEUTIC NEED[6,7,8,9]

The objective of treatment in type 2 diabetes is to reduce morbidity and mortality, in particular through correct glycaemic control. The short-term objective is the improvement of symptoms (thirst, polyuria, asthenia, emaciation and blurred vision) and prevention of acute complications (infections and hyperosmolar coma). The longer-term objective is the prevention of chronic microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (myocardial infarction, strokes and obliterating arteriopathy of the legs) complications and reduction of mortality.

According to the HAS guidelines (2013), the glycaemic target should be individualised depending on patient profile and can therefore change over time. Diabetes is progressive and treatment should be regularly re-assessed in all its components: lifestyle and dietary measures, therapeutic education and drug treatment. Data from literature does not enable a lower limit for the HbA1c target to be defined. Once the target is achieved, the treatment will be adjusted on a case-by-case basis. **For most patients with type 2 diabetes, an HbA1c target ≤ 7% is recommended.** The drug treatment should be initiated or re-assessed if the HbA1c is higher than 7%.

Special cases: for patients in whom diabetes has been newly diagnosed, with a life expectancy of more than 15 years and with no history of cardiovascular events, a target ≤ 6.5% is recommended, subject to it being achieved by the implementation or reinforcement of lifestyle and dietary measures then, in case of failure, by oral monotherapy.
In a certain number of particular cases, the glycaemic target is less demanding: age > 75 years; history of macrovascular complication; chronic renal failure; proven serious comorbidity; limited life expectancy (< 5 years); long-lasting diabetes (> 10 years) and whose target of 7% proves difficult to achieve because the increase in drugs risks inducing severe hypoglycaemia.

Implementation of effective lifestyle and dietary measures is a necessary prerequisite to drug treatment for glycaemic control.

Drug strategy:
According to the HAS guidelines (2013), as a general rule, the recommended strategy for introducing antidiabetic medicinal products is as follows:
- metformin monotherapy

[6] NICE (National Institute for Health and Clinical Excellence). NICE and diabetes: a summary of relevant guidelines. November 2009.
[7] SIGN (Scottish Intercollegiate Guidelines Network). Management of diabetes - A national clinical guideline. Guideline 116. March 2010.
[8] ADA (American Diabetes Association) and EASD (European Association for the Study of Diabetes). Inzucchi SE, Bergenstal RM, Buse JB, *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; 35: 1364-79.
[9] Stratégie médicamenteuse du contrôle glycémique du diabète de type 2 [Treatment strategy for glycaemic control of type 2 diabetes]. Recommandations de bonne pratique de la HAS [HAS Good practice guidelines]. January 2013.

- then, dual therapy metformin + sulfonylurea.

If the glycaemic target is not achieved despite dual therapy with metformin + sulfonylurea,

- ✓ if the deviation from the target is < 1% for HbA1c: triple therapy with metformin + sulfonylurea + alpha-glucosidase inhibitors or DPP-4 inhibitors.

- ✓ If the deviation from the target is > 1% for HbA1c, addition of insulin in combination with metformin + sulfonylurea or add a GLP-1 analogue as triple therapy in combination with dual therapy metformin +sulfonylurea if BMI ≥ 30 mg/m^2 or if weight gain on insulin is concerning.

In patients with elevated HbA1c levels (> 9.0%), dual therapy from the outset or insulin therapy can be offered as 1st-line treatment.
Some patients do not achieve or maintain the glycaemic targets with insulin therapy alone. It is therefore recommended to combine it with another antidiabetic. In practice, it is metformin which is widely used in combination with insulin.[10]
In the event of contraindications to or intolerance of metformin, sulfonylureas are offered. If, with these dual therapies, targets are not achieved, the doses of insulin can be increased but this increase in dose is often associated with an increased risk of hypoglycaemia and weight gain.

According to the HAS guidelines, during initiation of insulin treatment, DDP-4 inhibitors are discontinued. **As dual therapy, in combination with insulin, the other available gliptins such as sitagliptin,[12] linagliptin,[11] and saxagliptin[13] have no role in the therapeutic strategy for the management of patients with type 2 diabetes mellitus.**
If the targets are not achieved with these dual therapies, the doses of insulin can be increased but this increase in dose is often associated with an increased risk of hypoglycaemia and weight gain.

The gliptin + insulin + metformin triple therapy has not been addressed in the good practice guidelines updated by HAS in January 2013 on glycaemic control in type 2 diabetes.
However, linagliptin[11] or sitagliptin[12] are a treatment option that can be added to the combination of insulin + metformin in patients who do not achieve or maintain the glycaemic targets with a combination of insulin and metformin.
Given its low efficacy and the doubts about its safety profile, the role of saxagliptin as triple therapy has not been specified by the Committee, pending the re-assessment of all gliptins.[13]

[10] Nathan DM, Buse JB, Davidson MB, *et al.* Medical management of hyperglycaemia in type 2 diabetes mellitus: 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.
[11] Transparency Committee Opinion on TRAJENTA 5 mg. 20 March 2013.
[12] Transparency Committee Opinion on JANUVIA 100 mg. 18 July 2012.
[13] Transparency Committee Opinion on ONGLYZA 5 mg. 15 May 2013.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

NAME (INN) *Company*	Same TC* Yes/No	Indication in combination with insulin	Date of opinion	AB	IAB (Wording)	Reimbursement Yes/No
Biguanides						
GLUCOPHAGE Metformin Merck Santé And it's generics	No	Treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. In adults, GLUCOPHAGE may be used as monotherapy or in combination with other oral antidiabetic agents or with insulin. In children from 10 years of age and adolescents, GLUCOPHAGE may be used as monotherapy or in combination with insulin.	21 July 2010 (RI)	**Substantial**	-	Yes
Insulin secretagogues						
Sulfonylureas and their generics	No	Treatment of type 2 diabetes mellitus in the adult, when diet, physical exercise and weight reduction alone are not adequate for glycaemic control.		**Substantial**	-	Yes
DPP-4 inhibitors						
TRAJENTA 5 mg Film-coated tablet Linagliptin** Boehringer Ingelheim	Yes	Treatment of type 2 diabetes mellitus to improve glycaemic control in adults:[14] In combination with insulin with or without metformin, when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.	20 March 2013	**Insufficient** as dual therapy in combination with insulin **Substantial** as triple therapy in combination with insulin and metformin	V in treatment	No

[14] Linagliptin (TRAJENTA 5 mg) can be used in type 2 diabetic patients with renal impairment without dose adjustment. However, the proprietary medicinal product TRAJENTA 5 mg is not currently included on the list of medicines refundable by National Health Insurance or on the list of medicines approved for hospital use.

NAME (INN) *Company*	Same TC* Yes/No	Indication in combination with insulin	Date of opinion	AB	IAB (Wording)	Reimbursement Yes/No
ONGLYZA 5 mg Film-coated tablet Saxagliptin** Astra Zeneca	Yes	In adult patients aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control.[15] As combination therapy with insulin (with or without metformin), when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.	15 May 2013	**Insufficient** as dual therapy in combination with insulin **Low** as triple therapy in combination with insulin and metformin	V in treatment	Yes
JANUVIA/XELEVIA 25 mg, 50 mg[16] Film-coated tablet Sitagliptin MSD	Yes	As add-on to insulin (with or without metformin) when diet and exercise plus stable dose of insulin do not provide adequate glycaemic control.	19 September 2012	**Moderate** as dual therapy in combination with insulin **Insufficient** as dual therapy in combination with metformin	V in treatment	50 mg: Yes 25 mg: No
JANUVIA/XELEVIA 100 mg Film-coated tablet Sitagliptin** MSD	Yes	For adult patients with type 2 diabetes mellitus, to improve glycaemic control: As add-on to insulin (with or without metformin) when diet and exercise plus stable dose of insulin do not provide adequate glycaemic control.	18 July 2012	**Insufficient** as dual therapy in combination with insulin **Substantial** as triple therapy in combination with insulin and metformin	- V in treatment	Yes

*therapeutic category
**exists in fixed combination with metformin

[15] The dose of saxagliptin (ONGLYZA) must be reduced to 2.5 mg once daily in patients with moderate or severe renal impairment. This dose is not available in France.
[16] Dosages adjusted for patients with renal impairment. The 25 mg dose is not marketed in France.

06.2 Other health technologies

Not applicable.

Conclusion

As dual therapy in combination with insulin, the clinically relevant comparators are metformin and sulfonylureas.

As triple therapy in combination with insulin and metformin, the clinically relevant comparators are the DPP-4 inhibitor-based drugs: linagliptin, saxagliptin, sitagliptin.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Extensions of indication have only been approved in Europe.

Country	REIMBURSEMENT	
	YES/NO	Population(s) That of the Marketing Authorisation or restricted
Germany	Yes (100%)	Marketing Authorisation
United Kingdom	Yes (100%)	Marketing Authorisation
Italy	In progress	-
Spain	-	-
Portugal	In progress	-

08 SUMMARY OF PREVIOUS ASSESSMENTS

✓ **GALVUS:**

Date of Opinion (reason for the request)	10 December 10th 2008 (Inclusion)
Indication	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.
Actual Benefit	Substantial
Improvement in Actual Benefit	GALVUS provides no improvement in actual benefit (level V) in the management of patients with type 2 diabetes mellitus.
Studies requested	The Transparency Committee asks for a study to be carried out in a representative sample of French type 2 diabetic patients, treated with GALVUS. The aim of the study would be to describe the actual situation with regard to treatment: • the characteristics of the patients treated (including age, the HbA1c value at start of treatment, and renal, hepatic and cardiac function); • the conditions of use of this proprietary medicinal product (indication, dosage, concomitant treatments, etc.); • the level of maintenance of the treatment; • the frequency of discontinuations and the reasons for them; • the change in the HbA1c value and weight, and the occurrence of hypoglycaemia in the long-term (2 years).” Reasons should be given for the choice of study duration, which should be decided by a scientific committee, and the duration should be sufficiently long to meet the requests of the Transparency Committee. If scheduled or ongoing studies, in particular within the remit of the European Risk Management plan, do not answer all the questions raised by the Transparency Committee, a specific study must be conducted.

Date of Opinion (reason for the review)	November 7th 2012 (Extension of indication)
Indication	As monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.
Actual Benefit	Insufficient
Improvement in Actual Benefit	-
Studies requested	-

- ✓ **JALRA**

Date of Opinion (reason for the request)	September 7th 2011 (Inclusion)
Indication	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.
Actual Benefit	Substantial
Improvement in Actual Benefit	JALRA provides no improvement in actual benefit (level V) in the management of patients with type 2 diabetes mellitus.
Studies requested	The Transparency Committee had requested a study to be carried out in a representative sample of French type 2 diabetic patients treated with GALVUS. The proprietary medicinal product JALRA must be part of this post-inclusion monitoring.

09 ANALYSIS OF AVAILABLE DATA

The file from the company contains results from a double-blind, randomised, placebo-controlled study[17] in parallel groups, whose primary objective was to evaluate the efficacy and safety over 24 weeks of vildagliptin (50 mg twice daily) in combination with insulin in 449 type 2 diabetic (DT2) patients insufficiently controlled despite a stable dose of insulin (basal or premixed insulin) with or without metformin.

The company has also presented the data:

- from a randomised, double-blind, placebo-controlled study[18] in parallel groups, on 296 patients with advanced stage DT2, not controlled with insulin monotherapy used for more than 6 years (with elevated mean doses of around 82 IU/day, almost half the patients being on a complex regimen of 3 injections/day or more), whose objective was to evaluate the efficacy and safety of vildagliptin. as the patients did not receive metformin, which is not representative of clinical practice, this study is not presented.

- from a randomised, double-blind, placebo-controlled study,[19] whose objective was the evaluation of safety and efficacy over 24 weeks of vildagliptin versus placebo in 525 DT2 patients with moderate or severe renal impairment which resulted in the MA lifting the precautions for use in RI in 2012. The vildagliptin and placebo were given as monotherapy (for 3.7% of patients with moderate RI and 2.7% with severe RI) or combined with insulin (for 55.4% of patients with moderate RI and 69.2% of patients with severe RI) or with insulin and an OAD (for 12.9% of patients with moderate RI and 11.3% of patients with severe RI) or with an OAD alone or in combination. The primary objective was safety. The efficacy endpoints were exploratory. The safety data from this study have already been examined by the Committee as part of the extension of indication request for GALVUS/JALRA as monotherapy. The company presents a 1-year extension study[20] and a post-hoc analysis in 178 DT2 patients treated with insulin with severe renal impairment.[21] Due to their strictly exploratory nature, the efficacy data are not presented in this opinion.

09.1 Efficacy

Study of efficacy and safety over 24 weeks of vildagliptin + insulin ± metformin in DT2 patients insufficiently controlled despite a stable dose of insulin[17]

Principal study objective	To demonstrate superiority in terms of reducing HbA1c compared with the placebo in the complete analysis population. The analysis was also conducted in both populations, with and without metformin (secondary key objective).
Method	Multicentre, randomised, placebo-controlled, double-blind, 24-week study in parallel groups.
Study population	
Inclusion criteria	DT2 patients aged between 18 and 80 years, treated with stable doses of insulin (≤ 1 U/kg/day of basal, intermediate-acting or premixed insulin) with or

[17] Kothny W, Foley J, Kozlovski P, et al. Improved glycaemic control with vildagliptin added to insulin, with or without metformin, in patients with type 2 diabetes mellitus. Diabetes Obes Metab 15:252-257, 2013.
[18] Fonseca V, Schweizer A, Albrecht D, et al. Addition of vildagliptin to insulin improves glycaemic control in type 2 diabetes. Diabetologia 2007; 50(6): 1148-1155.
[19] Lukashevich V, Schweizer A, Shao Q, Groop PH, 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.
[20] Kothny W et al. One-year safety, tolerability and efficacy of vildagliptin in patients with type 2 diabetes and moderate or severe renal impairment. Diabetes Obes Metab 14: 1032-1039, 2012.
[21] Lukashevich V et al. Efficacy of vildagliptin in combination with insulin in patients with type 2 diabetes and severe renal impairment. Vascular Health and Risk Management 2013: 9 21-28.

	without metformin at a stable dose (≥ 1.5 g/day or maximum tolerated dose) for ≥ 12 weeks before the start of the study, with an HbA1c between 7.5 and 11%, a body mass index (BMI) of 22 to 40 kg/m^2 and a fasting blood sugar < 15 mmol/l.
Main non-inclusion criteria	Fasting glycaemia ≥ 15 mmol/l Acute metabolic complication Liver damage Recent cardiovascular history (myocardial infarction, coronary bypass or stroke or transient ischaemic attack in the last 6 months) Stage III or IV heart failure.
Study size and sites	67 centres across Europe, Asia, Australia, and Central America
Course of the study	After a 2-week selection period, the DT2 patients receiving a stable dose of basal, intermediate-acting or premixed insulin, with or without metformin, underwent balanced randomisation (1:1) to receive either vildagliptin 50 mg twice daily or a placebo. Inclusion of patients was stratified according to whether or not metformin was taken so as to ensure an approximate ratio of 60:40 (60% of patients with metformin, 40% of patients without metformin). Inclusion was stratified according to the type of insulin. After randomisation and the start of the study treatment, the patients were monitored with a visit every 4 weeks (at weeks 4, 8, 12, 16, 20 and 24) and had to continue their ongoing treatment with metformin (if applicable) and insulin (±10%) without any change unless adjustment was needed for safety reasons.
Primary efficacy endpoint	Adjusted change in HbA1c compared with baseline, at the end of the double-blind treatment period (week 24 or at the last available evaluation post-randomisation performed before any "major modification of insulin doses").
Secondary endpoints included:	Change in the fasting glycaemia compared with baseline Responder rate
Calculation of the number of subjects required	The calculation of the number of subjects required is based on a change of HbA1c compared with baseline of 1.1% at week 24, enabling a significant difference of 0.5% to be revealed with a power of 99% and one-sided alpha risk of 0.025 in patients treated with insulin with or without metformin. A sample of 386 patients was required (193 per group), therefore 428 patients to take into account lost to view (approximately 10%). Based on a 60:40 ratio, a sample of 428 patients would enable a significant difference of 0.5% to be revealed with power of 93% (subgroup with metformin) or 80% (subgroup without metformin) and a one-sided alpha risk of 0.025.
Statistical analysis	The primary efficacy endpoint was analysed using an analysis of covariance model (ANCOVA) with the treatment, region, use of metformin and type of insulin as factors and the initial HbA1c value as the covariate.

Results:

A total of 449 patients were randomised: 228 in the vildagliptin group and 221 in the placebo group.

Table 1: Analysis population - n (%)

	Vildagliptin	**Placebo**
Randomised	228 (100)	221 (100)
ITT population	224 (98.2)	216 (97.7)
Safety population	227 (99.6)	221 (100)
Per protocol population	206 (90.4)	196 (88.7)

A proportion of 91.2% (n=208) of patients from the vildagliptin group completed the study versus 86.4% (n=191) from the placebo group. More of the patients in the placebo group were lost to view (3.2% versus 0%) or left the study early due to consent withdrawal (5.4% versus 3.5%).

The early withdrawals for adverse events (AEs) were 3.9% on vildagliptin and 1.8% on placebo. One single death occurred in the placebo group.

At inclusion, the demographic characteristics of the patients were homogeneous in both treatment groups with a mean age of 59.2 years (30% ≥ 65 years), a proportion of obese patients 38.3% (mean BMI 28.9 kg/m^2), a mean length of the disease of 13 years and the mean initial HbA1c as 8.8%. Fasting glycaemia was slightly higher in the vildagliptin group (9.6 versus 9.1 mmol/l).

At inclusion, insulin treatment was comparable in both groups: with ~60% of patients on premixed insulin, ~23% on basal insulin, and ~17% on intermediate-acting insulin. The mean number of injections per day (1.8 in each group), the length of insulin treatment (4.4 years in each group) and the mean daily dose of insulin (39.9 and 41.9 units/day in the vildagliptin and placebo groups respectively) were balanced. A total of 276 patients (61.5%) received concomitant treatment with metformin (at a daily dose of around 2 g/day) and 173 (38.5%) were treated with insulin alone.

Almost 70% of study patients received an antihypertensive treatment and half of then received a lipid-lowering treatment (mainly with statins). 22% of included patients also presented cardiac history.

Primary endpoint

In the overall study population, after 24 weeks, the treatment with vildagliptin in addition to a stable dose of insulin (with or without metformin) demonstrated a significant reduction of HbA1c of -0.77% with a difference versus placebo of -0.72±0.1% (p<0.001).

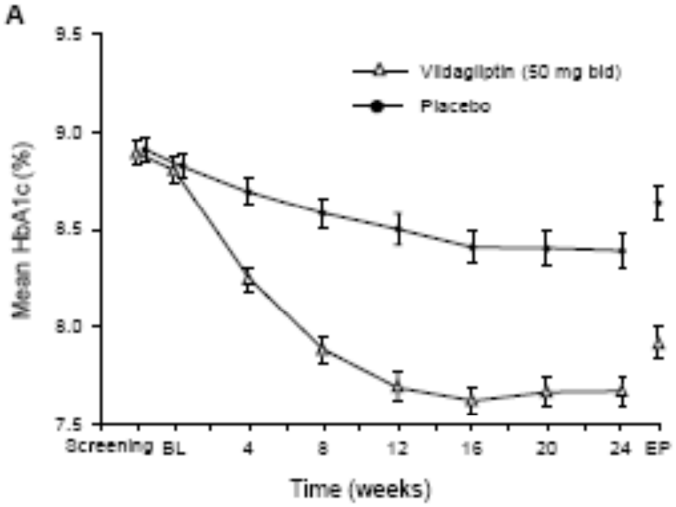

Figure 1: Mean level (±SE) of HbA1c during the 24 weeks of treatment in patients treated with insulin in the vildagliptin group (∆) or placebo group (●).

- Subgroup analysis with or without concomitant metformin

The mean reduction of HbA1c versus placebo was -0.63±0.1% (p<0.001) in the subgroup of the 267 patients treated with triple therapy (vildagliptin+insulin+metformin) and -0.84%±0.2% (p<0.001) in the subgroup of 169 patients on dual therapy (vildagliptin+insulin).

Table 2: ANCOVA results of the adjusted change in HbA1c compared with baseline and the end of treatment period (total population)

				Difference of the adjusted means		
Treatment	n	Initial HbA1c Mean (SE)	Mean adjusted reduction (SE)	Mean (SE)	95% CI	p
Total analysis						
Vildagliptin 50 mg 2/day	221	8.80 (0.07)	-0.77 (0.08)	-0.72 (0.10)	(-0.92, -0.52)	<0.001

Placebo	215	8.84 (0.07)	-0.05 (0.08)			
Total analysis (insulin+met)						
Vildagliptin 50 mg 2/day	133	8.78 (0.08)	-0.98 (0.09)	-0.63 (0.12)	(-0.86, -0.39)	<0.001
Placebo	134	8.80 (0.08)	-0.35 (0.09)			
Total analysis (insulin)						
Vildagliptin 50 mg 2/day	88	8.84 (0.12)	-0.60 (0.19)	-0.84 (0.19)	(-1.21 , -0.47)	<0.001
Placebo	81	8.90 (0.11)	0.24 (0.20)			

Secondary endpoints

At inclusion, the mean fasting glycaemia was similar in both groups with 9.84 mmol/l in the vildagliptin group versus 9.50 mmol/l in the placebo group. The fasting glycaemia reduced in the vildagliptin treatment arm by -0.77 mmol/l and -0.18 mmol/l in the placebo arm, with a difference vs. placebo of -0.59 mmol/l (p=0.05).

In the overall study population, the proportions of patients having achieved HbA1c < 7% was higher on vildagliptin than on placebo: 22.2% (49/221) versus 5.1% (11/214) (p<0.001).

09.2 Safety/Adverse effects

9.2.1 Clinical study data

- **Study of efficacy and safety over 24 weeks of vildagliptin + insulin ± metformin in DT2 patients insufficiently controlled despite a stable dose of insulin[17]**

The exposure to treatment was 23.1 weeks in the vildagliptin group versus 22.8 weeks in the placebo group.
Adverse events (AE) were reported in 57.7% of patients in the vildagliptin group and 47.5% of patients in the placebo group (Table 3).

Table 3: Number (%) of patients reporting the most common AEs (> 4% in one of the two groups) (Safety Population)

	Vildagliptin 50 mgx2/day + Insulin N=227 n (%)	**Placebo + Insulin N=221 n (%)**
All AEs	**131 (57.7)**	**105 (47.5)**
Hyperhidrosis	26 (11.5)	28 (12.7)
Hypoglycaemia	19 (8.4)	16 (7.2)
Dizziness	18 (7.9)	19 (8.6)
Tremors	16 (7.0)	11 (5.0)
Upper respiratory tract infections	16 (7.0)	7 (3.2)
Diarrhoea	10 (4.4)	4 (1.8)
Asthenia	8 (3.5)	10 (4.5)
Fatigue	4 (1.8)	9 (4.1)

The percentage of patients who had an AE resulting in study withdrawal was 4.0% in the vildagliptin group and 2.3% in the placebo group. The SAEs were rare and were reported as a similar percentage of patients in both groups: 4.0% vs. 4.1% in the vildagliptin and placebo groups respectively. The majority of SAEs were isolated events occurring in a single patient.

Cardiovascular and cerebrovascular events were confirmed by an independent adjudication committee[22] for five patients in total: one (0.48%) patient in the vildagliptin and four patients (1.8%) in the placebo group.
A single patient died during the study: one patient from the placebo group, following ketoacidosis.
The incidence of hypoglycaemia was 8.4% on vildagliptin and 7.2% on the placebo. The total number of hypoglycaemic episodes reported in the vildagliptin group (51) was higher than in the placebo group (36); the difference was mainly due to several patients having presented recurrent episodes (> 2 episodes): four patients in the vildagliptin group reported a total of 35 hypoglycaemic episodes and five patients from the placebo group had 24 episodes. The majority of hypoglycaemic episodes were classified as mild (90.2% and 94.4% of the hypoglycaemic episodes on vildagliptin and placebo respectively). The severe hypoglycaemic episodes requiring assistance from another person were rare (two cases (0.9%) in each group).

- **Study in a DT2 population with renal impairment (reminder about the data in the Committee opinion dated 21/11/2012)**

Objective and methodology: phase III, 2:1 randomised, double-blind, placebo-controlled 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 a previously received antidiabetic treatment in 525 patients with insufficiently controlled type 2 diabetes mellitus, with moderate (n=294) or severe (n=221) renal impairment after 24 weeks of treatment.

The protocol planned for stratified randomisation, in particular according to the level of severity of the renal impairment.
The endpoints (change in HbA1c level, responder rate) were exploratory endpoints.

Inclusion criteria:
Patients with type 2 diabetes mellitus aged over 18 years, insufficiently controlled (HbA1c level ≥ 6.5% and ≤ 10%) and not having received antidiabetic treatment for at least 8 weeks, or receiving stable treatment for at least 4 weeks in particular with a sulfonylurea, glinide, an alpha-glucosidase inhibitor or insulin, alone or in combination.
Patients with cardiovascular history (myocardial infarction, unstable angina, CVA) in the last 6 months were not included in the study.

Dosing regimen:
525 patients were randomised to receive in addition to their previous 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:
At inclusion, the characteristics of the patients in the two treatment groups were similar.
In the group of patients with moderate RI, the patients had a mean age of 68.6 years (more than 70% of patients were over 65 years), were obese, diabetic for 15.1 years, with an HbA1c level of 7.8% and more than 2/3 of them were being treated with insulin alone or in combination with oral antidiabetic drugs.
In the group of patients with severe RI, the patients had a mean age of 64.3 years (50.7% of patients were over 65 years), were obese, diabetic for 18.1 years, with an HbA1c level of 7.7% and more than 3/4 of them were being treated with insulin alone or in combination with oral antidiabetic drugs.
Dual therapy with insulin involved 55.4% (n=163/294) of the patients with moderate RI (95 on vildagliptin and 68 on placebo) and 69.2% (n=153/221) of patients with severe RI (87 on vildagliptin and 66 on placebo).

[22] An independent adjudication committee (made up of five cardiologists and one neurologist) carried out a prospective evaluation, without unblinding, of any potential cardiovascular and cerebrovascular (CCV) event occurring during clinical trials in phase III of the development plan.

Insulin rescue treatment (planned in the protocol in case of insufficient glycaemic control, in addition to ongoing treatment or treatment intensification) involved 9 patients on vildagliptin and 13 on placebo and in the patients with moderate RI, 1 patient on vildagliptin and 3 on placebo in the patients with severe RI.

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

Table 4: Main observed adverse events:

Type of adverse events	Moderate RI n (%)		Severe RI N (%)	
	Vildagliptin N=163	Placebo n=129	Vildagliptin N=124	Placebo 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)
Metabolism 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)
Muscular disorders	25 (15.3)	20 (15.5)	9 (7.3)	14 (14.4)
Gastrointestinal complaints	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)

In patients with moderate RI, the treatment discontinuations for adverse events involved 4 patients on vildagliptin, 7 on placebo; in the patients with severe RI, 11 patients on vildagliptin and 6 on placebo.
There was no particular report of hepatic, skin, oedema and pancreatitis adverse events.
The most common observed adverse events were hypoglycaemia, infections (mainly nasopharyngitis) and peripheral oedema.
Concerning the cardiovascular safety, one case of syncope was identified in one patient with severe RI. Three hepatic events (AST/ALT level > 5 ULN) were reported in one patient with moderate RI on vildagliptin and two patients on placebo.

This study was followed by a 1-year extension which did not reveal any particular signals.[20]

9.2.2 Data from the last PSUR (period from 01/03/2011 to 29/02/2012) in all the vildagliptin indications

The company provided data from the latest international PSUR for vildagliptin which had already been assessed by the Committee as part of the extension of indication assessment as monotherapy (Transparency Committee opinion dated 21 November 2012). The global exposure to the proprietary medicinal product GALVUS can be estimated at 1.12 million patient-years from February 2007 to 28 February 2012.

9.2.3 SPC data

- **Adverse effects reported in patients having received GALVUS/JALRA 100 mg/day in combination with insulin (with or without metformin) in double-blind studies (N=371):**

Metabolism and nutrition disorders
Common Decreased blood glucose
Nervous system disorders
Common Headache, chills

Gastrointestinal disorders

Common	Nausea, gastroesophageal reflux
Uncommon	Diarrhoea, flatulence

- **Post-marketing adverse effects**

Gastrointestinal disorders

Undetermined	Pancreatitis

Hepatobiliary disorders

Undetermined	Hepatitis (reversible after discontinuation of medicine)
	Abnormalities on the hepatic function tests (reversible after discontinuation of medicine)

Skin and subcutaneous tissue disorders

Undetermined	Urticaria
	Bullous or desquamating skin lesions

9.2.4 RMP data[23]

The identified risks are: elevated transaminases and drug-induced liver injury, angioedema, acute pancreatitis, skin lesions and hypoglycaemia.
The potential risks are: serious infections, cardiac events in patients with heart failure (NYHA III), muscle events with or without use of a statin, neuropsychiatric events and breast cancer.

9.2.5 National monitoring

In France, in the extension of the European RMP, ANSM [French National Agency for Medicines and Health Products Safety] implemented incretin mimetic national monitoring. In this context, the[24] French comité technique de pharmacovigilance (CT) (pharmacovigilance technical committee) recalled that "Diabetes mellitus is a disease with increased risk of pancreatitis or pancreatic cancer. Following the publication by Butler et al.[25] in March 2013 revealing, on a very limited series of autopsies, alpha and beta pancreatic hyperplasia with cellular proliferation of the pancreas in diabetic subjects treated with incretin-based drugs compared with non-diabetic patients or patients treated with other drugs, an arbitration procedure according to article 5.3 has been initiated on a European level to assess all the preclinical elements, clinical trials and pharmacovigilance data on the risk of pancreatitis and pancreatic cancer. Concerning the risk of pancreatic cancer, and due to the absence of sufficiently robust scientific proof, the addition of the "cancer" statement in the SPC has not been supported by the CT members. The results of the long-term studies on morbidity and mortality and cardiovascular safety are still pending, to which the complete elements of pancreatic safety must be added".

09.3 Usage/prescription data

According to the IMS data (moving annual total, spring 2014), 207,150 prescriptions were written for GALVUS. The proprietary medicinal product JALRA does not appear in this panel.

[23] Version 10.1 dated 08 August 2012
[24] ANSM. Meeting of the Comité technique de pharmacovigilance-CT012013043. 18 June 2013.
[25] Marked Expansion of Exocrine Pancreas with Incretin Therapy in Humans with Increased Exorcine Pancreas Dysplasia and the Potential for Glucagon-Producing Neuroendocrine Tumors. Diabetes. March 2013.

09.4 Summary and discussion

Vildagliptin in combination with insulin therapy, with or without metformin in type 2 diabetes, was evaluated in a randomised double-blind study versus placebo in 449 patients with type 2 diabetes insufficiently controlled with insulin, with or without metformin.
The included patients had a mean age of 59.2 years (30% ≥ 65 years) and 38.3% were obese.
The average HbA1c level at inclusion was 8.8%.
All patients were treated with insulin. The length of treatment with insulin was 4.4 years in each group. A proportion of 61.5% of patients (n=276) were receiving dual therapy with insulin + metformin (around 2 g/day) and 38.5% (n=173) monotherapy insulin. The low proportion of patients on dual therapy do not enable the benefit of the insulin + vildagliptin combination to be demonstrated in patients with type 2 diabetes. In combination with insulin, a study versus metformin or versus sulfonylurea (reference comparators) would enable the benefit and contribution of vildagliptin to be specified. As triple therapy, only 61.5% of included patients corresponded to this indication. In this indication, a comparison group with an optimised insulin therapy regimen would have been useful to determine the addition of vildagliptin in combination with insulin and metformin. In DT2 patients with renal impairment, we only have the results from exploratory efficacy with vildagliptin versus placebo after 24 weeks in 294 patients with moderate RI and 221 with severe RI.

After 24 weeks of treatment, the reduction in HbA1c level was greater with vildagliptin + insulin ± metformin than with the placebo + insulin ± metformin (difference between vildagliptin and placebo: -0.72%, 95% CI [-0.92; -0.52]; p<0.001).
According to a subgroup analysis, the mean reduction of HbA1c versus placebo was:
- -0.63 ± 0.1% (p<0.001) in the subgroup of 267 patients on vildagliptin as triple therapy (+ insulin + metformin),
- -0.84 ± 0.2% (p<0.001) in the subgroup of 169 patients on vildagliptin as dual therapy (+ insulin),

Concerning the secondary endpoints, in the overall study population, the fasting glycaemia reduced in the vildagliptin group compared with the placebo group (difference versus placebo: -0.59 mmol/l (p=0.05)). The patient responder rate (HbA1c level < 7%) was higher on vildagliptin than on placebo with 22.2% versus 5.1% (p<0.001).

Adverse events (AE) were reported in 57.7% of patients in the vildagliptin group and 47.5% of patients in the placebo group. The most common adverse events (> 5% of patients) observed in the vildagliptin group were hyperhidrosis, hypoglycaemia, dizziness, tremors, upper respiratory tract infection.
The incidence of hypoglycaemia was 8.4% on vildagliptin and 7.2% on placebo. Severe hypoglycaemic episodes were rare (two cases (0.9%) in each group).

The most commonly observed adverse events in the specific population of DT2 patients with renal impairment were: hypoglycaemia, infections (mainly nasopharyngitis) and peripheral oedema. In the population of DT2 patients with renal failure, the available efficacy data are exploratory because they are based on a secondary endpoint or post-hoc analyses of subgroups.

In addition, as triple therapy in combination with insulin and metformin, it is impossible to assess patients with severe renal impairment, since metformin is contraindicated in these patients.

09.5 Planned studies

In its opinion dated December 10th 2008, the Transparency Committee requested a study to be carried out in a representative sample of French type 2 diabetic patients, treated with GALVUS. The objectives of the VILDA observational study are to describe the real treatment situation and over 2 years:

- the characteristics of the patients treated with vildagliptin (including age, the HbA1c value at the start of treatment, and renal, hepatic and cardiac function);
- the conditions of use of vildagliptin (indication, dosage, concomitant treatments, etc.);
- the level of maintenance of treatment;
- the frequency of discontinuations and the reasons for them;
- the change in the HbA1c value and weight, and the occurrence of hypoglycaemia in the long-term (2 years).

The final report for this study has been submitted and will be examined by the Transparency Committee as part of the inclusion renewal for the GALVUS/JALRA proprietary medicinal products.

010 THERAPEUTIC USE

Gliptins (including vildagliptin) have no role in therapeutic strategy for the management of type 2 diabetic patients as dual therapy in combination with insulin.

As triple therapy, vildagliptin is a treatment option that can be added to the combination of insulin + metformin in patients who do not achieve or maintain the glycaemia targets with a combination of insulin and metformin.

This treatment situation (triple therapy of a gliptin in combination with insulin and metformin) is for patients who cannot be treated with a sulfonylurea.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual benefit

11.1.1 As dual therapy in combination with insulin:

◗ Type 2 diabetes is a chronic disease with potentially serious complications, particularly cardiovascular complications.
◗ GALVUS/JALRA is used in the context of treatment for hyperglycaemia.
◗ In view of:
- the absence of clinical practice guidelines on this dual therapy and the fact that the only antidiabetics recommended in combination with insulin and used in practice are metformin and sulfonylureas,
- the absence of any study comparing the insulin + vildagliptin combination versus insulin + metformin or versus insulin + sulfonylurea which could have enable to quantifythe benefit and contribution of this dual therapy,
- the small number of patients treated with insulin alone (38.5%) in the study comparing vildagliptin with a placebo, in combination with insulin,
- the exploratory efficacy data in renal impairment patients,

the efficacy/adverse effect ratio for GALVUS/JALRA as dual therapy in addition to insulin cannot be qualified.
◗ In view of the available data, this proprietary medicinal product cannot be recommended as dual therapy in combination with insulin. In fact, when initiating insulin treatment, metformin is the reference treatment to combine with it. According to the guidelines, when insulin therapy is started

to maintain or improve glycaemic control, the following dual therapies, insulin + metformin or insulin + sulfonylurea, are the validated combinations.

Public health benefit:

The public health burden of type 2 diabetes is substantial because of its high prevalence, which is constantly increasing, and the associated microvascular and macrovascular complications. The public health burden in the subpopulation of patients with an indication for GALVUS/JALRA as dual therapy is considered to be moderate.

The improvement of the therapeutic management of type 2 diabetics represents a public health need which comes within the framework of established priorities.[26] Access to effective treatments which are well tolerated in type 2 diabetes patients is a public health need.

The proprietary medicinal product GALVUS/JALRA is not likely to present a public health benefit for this extension of indication as dual therapy, in combination with insulin, given the absence of any additional impact on the public health criteria (morbidity and mortality data, improved quality of life) compared with the current management of type 2 diabetes.

Consequently, the Committee considers that the actual benefit of GALVUS/JALRA as dual therapy, in combination with insulin, when this treatment alone, with diet and exercise, does not provide adequate glycaemic control, is insufficient for reimbursement by National Health Insurance.

11.1.2 As triple therapy in combination with insulin and metformin

◗ Type 2 diabetes is a chronic disease with potentially serious complications, particularly cardiovascular complications.
◗ GALVUS/JALRA is used in the context of treatment for hyperglycaemia.
◗ The efficacy/adverse effect ratio for GALVUS/JALRA as dual therapy in combination with insulin and metformin is moderate.
◗ It is a treatment to be used as triple therapy after failure of the metformin + insulin combination, in patients who cannot be treated with a sulfonylurea.
◗ There are treatment alternatives to this proprietary medicinal product.

◗ Public health benefit:

The public health burden of type 2 diabetes is substantial because of its high prevalence, which is constantly increasing, and the associated microvascular and macrovascular complications. The burden represented on the sub-population of patients for whom GALVUS/JALRA is indicated as triple therapy is moderate.

Improvement in the treatment of type 2 diabetics represents a public health need which comes within the framework of established priorities.[26]

The GALVUS/JALRA proprietary medicinal product is not likely to present a public health benefit for this extension of indication as triple therapy, in combination with insulin and metformin, given the absence of any additional impact on the public health criteria (morbidity and mortality data, improved quality of life) compared with the current management of type 2 diabetes.

Consequently, the Committee considers that the actual benefit of GALVUS/JALRA is moderate in combination with insulin and metformin, when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control.

✓ **As dual therapy in combination with insulin:**

[26] Objective 55 of the Law of 9 August 2004 relating to the public health policy: Reducing the frequency and severity of the complications of diabetes, particularly cardiovascular complications, a national improvement plan for the quality of life of persons with from chronic diseases 2007-2011.

The Committee does not recommend inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in this extension of indication and at the dosages in the Marketing Authorisation.

- ✓ **As triple therapy in combination with insulin and metformin:**

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and/or on the list of medicines approved for hospital use in this extension of indication and at the dosages in the Marketing Authorisation.

◗ **Proposed reimbursement rate: 30%**

011.2 Improvement in actual benefit (IAB)

- ✓ **As dual therapy in combination with insulin:**

Not applicable.

- ✓ **As triple therapy in combination with insulin and metformin:**

In the absence of direct comparative data versus an active comparator, the Transparency Committee considers that GALVUS/JALRA does not provide any improvement in actual benefit (level V, non-existent) in the treatment of patients with type 2 diabetes in combination with insulin and metformin, in patients not achieving or maintaining the glycaemic targets on a combination of insulin + metformin.

011.3 Target population

The target population corresponds to patients with type 2 diabetes treated with vildagliptin **as triple therapy in combination with insulin and metformin**, in patients not achieving or not maintaining the glycaemic targets on a combination of insulin + metformin and who cannot be treated with sulfonylureas.

The target population of the DPP-4 inhibitors in combination with insulin and metformin (**triple therapy**) is said to be around **113,000 patients.**[27]

The target population of GALVUS/JALRA, in addition to insulin and metformin lies within this population.

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ **Packaging**

Appropriate for the prescribing conditions according to the indication, dosage and treatment duration.

[27] Transparency Committee Opinion of 20 March 2013 – TRAJENTA.