HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
1 October 2014

VIPIDIA 6.25 mg, film-coated tablet
B/28 tablets (CIP: 34009 276 963 8 1)
VIPIDIA 12.5 mg, film-coated tablet
B/28 tablets (CIP: 34009 276 964 4 2)
VIPIDIA 25 mg, film-coated tablet
B/28 tablets (CIP: 34009 276 965 0 3)

Applicant: TAKEDA

INN	alogliptin
ATC Code (2014)	A10BH04 (Blood glucose lowering drugs, excl. insulins)
Reason for the request	**Inclusion**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"VIPIDIA is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control in combination with other glucose lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control."**

Actual Benefit	- **Substantial as dual therapy in combination with metformin,** - **Substantial as dual therapy in combination with a sulfonylurea,** - **Insufficient as dual therapy in combination with insulin,** - **Insufficient as triple therapy in combination with metformin and a sulfonylurea,** - **Moderate as triple therapy in combination with metformin and insulin.**
Improvement in Actual Benefit	**<u>In the indications as dual therapy in combination with metformin or a sulfonylurea and as triple therapy in combination with metformin and insulin:</u>** **Given the absence of demonstrated superiority compared with available oral antidiabetics, and in the absence of data on the long-term safety, the Committee considers that the VIPIDIA proprietary medicinal products do not provide any improvement in actual benefit (level V, non-existent) in the management of patients with insufficiently controlled type 2 diabetes mellitus as dual oral therapy in combination with metformin or a sulfonylurea, and as triple therapy in combination with metformin and insulin.** **<u>In the indications as dual therapy in combination with insulin and as triple therapy in combination with metformin and a sulfonylurea:</u>** **Not applicable.**
Therapeutic use	**Alogliptin is a supplementary therapeutic agent in insufficiently controlled type 2 diabetes mellitus:** - **as dual therapy in combination with metformin, from the available oral antidiabetics, in case of intolerance or contraindication to sulfonylureas,** - **as dual therapy in combination with a sulfonylurea, from the available oral antidiabetics, in case of intolerance or contraindication to metformin,** - **as triple therapy in combination with metformin and insulin.** **In the absence of data, alogliptin cannot be recommended as triple therapy with metformin and a sulfonylurea.** **Given the transposability difficulties and the absence of recommendations, alogliptin can no longer be recommended as dual therapy with insulin.**
Recommendations	

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Date initiated: 19 September 2013 (centralised procedure, rapporteur: Netherlands);
Prescribing and dispensing conditions/special status	List I

ATC Classification	2014	
	A	Alimentary tract and metabolism
	A10	Drugs used in diabetes
	A10B	Blood glucose lowering drugs, excl. insulins
	A10BH	Dipeptidyl peptidase 4 (DPP-4) inhibitors
	A10BH04	alogliptin

02 BACKGROUND

This is a request for inclusion of the VIPIDIA proprietary medicinal products, oral antidiabetics, on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use, in the indication of treatment in adult patients with insufficiently controlled type 2 diabetes mellitus, in combination with other glucose lowering medicinal products including insulin.

The active ingredient of VIPIDIA is alogliptin which is a dipeptidylpeptidase-4 (DPP-4) inhibitor, the 5th of this class.

03 THERAPEUTIC INDICATIONS

"**VIPIDIA is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control in combination with other glucose lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations).**"

04 DOSAGE

"Dosage

For the different dose regimens, VIPIDIA is available in strengths of 25 mg, 12.5 mg and 6.25 mg film-coated tablets.

Adults (≥ 18 years old)
The recommended dose of alogliptin is one tablet of 25 mg once daily as add-on therapy to metformin, a thiazolidinedione, a sulfonylurea, or insulin or as triple therapy with metformin and a thiazolidinedione or insulin.
When alogliptin is used in combination with metformin and/or a thiazolidinedione, the dose of metformin and/or the thiazolidinedione should be maintained, and VIPIDIA administered concomitantly.

When alogliptin is used in combination with a sulfonylurea or insulin, a lower dose of the sulfonylurea or insulin may be considered to reduce the risk of hypoglycaemia (see section 4.4).

Caution should be exercised when alogliptin is used in combination with metformin and a thiazolidinedione as an increased risk of hypoglycaemia has been observed with this triple therapy (see section 4.4). In case of hypoglycaemia, a lower dose of the thiazolidinedione or metformin may be considered.

The safety and efficacy of alogliptin when used as triple therapy with metformin and a sulfonylurea have not been fully established.

Special populations

Elderly (≥ 65 years old)
No dose adjustment is necessary based on age. However, dosing of alogliptin should be conservative in patients with advanced age due to the potential for decreased renal function in this population.

Renal impairment
For patients with mild renal impairment (creatinine clearance > 50 to ≤ 80 mL/min), no dose adjustment of alogliptin is necessary (see section 5.2).

For patients with moderate renal impairment (creatinine clearance ≥ 30 to ≤ 50 ml/min), one-half of the recommended dose of alogliptin should be administered (12.5 mg once daily; see section 5.2).

For patients with severe renal impairment (creatinine clearance < 30 ml/min) or end-stage renal disease requiring dialysis, one-quarter of the recommended dose of alogliptin should be administered (6.25 mg once daily). Alogliptin may be administered without regard to the timing of dialysis. Experience in patients with severe renal impairment or end-stage renal disease requiring dialysis is limited and alogliptin must be used with caution in these patients (see sections 4.4 and 5.2):

Appropriate assessment of renal function is recommended prior to initiation of treatment and periodically thereafter (see section 4.4).

Hepatic impairment
No dose adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh scores of 5 to 9). Alogliptin has not been studied in patients with severe hepatic impairment (Child-Pugh score > 9) and is, therefore, not recommended for use in such patients (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of VIPIDIA in children and adolescents < 18 years old have not been established. No data are available. No data are available.

Method of administration

Oral use.

VIPIDIA should be taken once daily with or without food. The tablets should be swallowed whole with water.

If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day. "

05 THERAPEUTIC NEED[1,2,3,4]

The objective of treatment in type 2 diabetes mellitus 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 peripheral arterial disease of the legs) complications and reduction of mortality.

According to the HAS guidelines in 2013,[4] the glycaemic target of patients with type 2 diabetes mellitus is to be defined for each patient depending on comorbidities and life expectancy: the HbA1c target varies between 6.5% and 8 %. For the majority of patients, it turns out that a target HbA1c less than or equal to 7% is recommended. </257 The drug treatment should be initiated or re-assessed if the HbA1c is higher than 7%. Diabetes mellitus is progressive and treatment should be regularly re-assessed in all its components: lifestyle and dietary measures, therapeutic education and drug treatment.

Special cases: for patients in whom diabetes mellitus has been newly diagnosed, with a life expectancy of more than 15 years and with no history of cardiovascular events, a target of ≤ 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.
There is a certain number of special cases where 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 causes severe hypoglycaemia.
The implementation of effective lifestyle and dietary measures is a necessary prerequisite to drug treatment for glycaemic control.

Drug strategy:
According to the HAS guidelines, if the glycaemic target is not achieved despite the implementation of lifestyle and dietary measures, monotherapy must be started with metformin as first-line treatment or, in case of contraindications, sulfonylureas (if these two substances are contraindicated, repaglinide or alpha-glucosidase inhibitors are recommended).

Combinations recommended as dual therapy:
If the glycaemic target is not achieved with monotherapy, dual therapy is recommended combining metformin and sulfonylureas as first-line treatment, while monitoring the weight and occurrence of hypoglycaemia.

In the event of intolerance or contraindication to sulfonylureas, and if the deviation from the target is less than 1% for HbA1c, the following treatment regimens may be proposed:

[1] NICE (National Institute for Health and Clinical Excellence). NICE and diabetes: a summary of relevant guidelines. November 2009.
[2] SIGN (Scottish Intercollegiate Guidelines Network). Management of diabetes - A national clinical guideline. Guideline 116. March 2010.
[3] 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.
[4] Stratégie médicamenteuse du contrôle glycémique du diabète de type 2 [Treatment strategy for glycaemic control of type 2 diabetes mellitus]. Recommandations de bonne pratique de la HAS [HAS Good practice guidelines]. January 2013.

- metformin + repaglinide combination (if irregularity in intake of food),
- metformin + alpha-glucosidase inhibitor combination (if the occurrence of hypoglycaemia is of concern),
- metformin + dipeptidyl peptidase-4 inhibitors/gliptins combination (if the occurrence of hypoglycaemia or the increase in weight are of concern).

In the event of intolerance or contraindication to metformin, and if the deviation from the target is less than 1% for HbA1c, the following treatment regimens may be proposed:

- sulfonylurea + alpha-glucosidase inhibitor combination,
- sulfonylurea + DPP-4 inhibitor combination.

The use of GLP-1 analogues is possible at the dual therapy stage if the BMI is greater than or equal to 30 kg/m^2 or if the increase in weight on insulin or the occurrence of hypoglycaemia are of concern.

Combinations recommended as triple therapy:

If the glycaemic target is not achieved despite metformin + sulfonylurea dual therapy and if the deviation from the target is less than 1% for HbA1c, the following treatment regimens can be proposed:

- metformin + sulfonylurea + alpha-glucosidase inhibitor combination
- metformin + sulfonylurea + DPP-4 inhibitor/gliptin combination.

Insulin therapy and combination:

In patients with elevated HbA1c levels (> 9.0%), dual therapy from the outset or insulin therapy can be offered as first-line treatment.

Some patients do not achieve or maintain 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.[5]

In the event of contraindications or intolerance to 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, DPP-4 inhibitors are discontinued. **As dual therapy, in combination with insulin, the other available gliptins such as sitagliptin,**7 **linagliptin,**6 **and saxagliptin have no role in the therapeutic strategy for the management of patients with type 2 diabetes mellitus.**

If the targets are not achieved with dual therapy, 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 mellitus.

Linagliptin[6] or sitagliptin[7] are a treatment option that can be added to the combination of insulin + metformin in patients who do not achieve or maintain glycaemic targets with a combination of insulin and metformin.

In patients with moderate renal impairment (RI), in the case of contraindication to sulfonylureas, dual therapy from the outset with insulin/sitagliptin 50 mg is possible.[8]

In patients with chronic, severe renal impairment, the only authorised therapeutic classes are insulin, repaglinide, alpha-glucosidase inhibitors up to 25 ml/min and DPP-4 inhibitors at an appropriate dosage.

[5] 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.

[6] Transparency Committee Opinion on TRAJENTA. 20 March 2013.

[7] Transparency Committee Opinion on JANUVIA. 18 July 2012.

[8] Transparency Committee Opinion on JANUVIA. 19 September 2012.

In cases of severe renal impairment or end-stage renal disease, dual therapy from the outset with insulin/sitagliptin at a dosage of 25 mg is a possible alternative to insulin on its own or to the insulin + glinide combination.

Sodium/Glucose transporter 2 inhibitors

To date, this new therapeutic class includes three drugs: dapagliflozin, canagliflozin and empagliflozin. No international guidelines include the prescription of this class of drugs.

According to the opinion of the Transparency Committee,[9] dapagliflozin is not recommended as monotherapy or dual therapy with insulin; however, it is a supplementary therapeutic agent, as dual therapy with metformin or sulfonylureas or as triple therapy after failure of the insulin/metformin combination. Canagliflozin and empagliflozin are being assessed by the Committee.

[9] Transparency Committee Opinion of 23 April 2014 for FORXIGA.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

These are proprietary medicinal products indicated **in combination,** in the treatment of type 2 diabetes mellitus in patients with inadequate glycaemic control at maximum tolerated doses of the following medicinal products (in combination with lifestyle and dietary measures):

- metformin in combination with sulfonylureas, then, in the case of failure, glinides, alpha-glucosidase inhibitors, gliptins (oral), GLP-1 analogues (injectable) or dapagliflozin;
- sulfonylureas in combination with metformin or, in the case of contraindication or intolerance to metformin, in combination with dapagliflozin, alpha-glucosidase inhibitors, gliptins or GLP-1 analogues;
- insulin in combination with an oral antidiabetic: metformin, sulfonylureas, GLP-1 analogues or dapagliflozin (triple therapy with metformin).

Comparators are presented in the appendix of this document.

06.2 Other health technologies

Not applicable.

◗ Conclusion

The listed comparators are all clinically relevant.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

The VIPIDIA proprietary medicinal products obtained MA in 2013 in Europe and the USA and in 2010 in Japan.

COUNTRY	Marketing Authorisation		REIMBURSEMENT	
	Date	Indications	YES/NO	Populations
Switzerland	21 Nov 2013	Treatment in combination with metformin, a sulfonylurea or insulin (with or without metformin)	21 November 2013	Marketing Authorisation
Europe	19 Sept 2013	VIPIDIA is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control in combination with other glucose lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations).	Denmark 25 Nov 2013	Marketing Authorisation
			United Kingdom 27 January 2014	Marketing Authorisation
			Austria, Norway Sweden, Italy, Belgium, Spain: under assessment	-
United States	25 Jan 2013	Type 2 diabetes mellitus Patients with an insufficient response to: 1) Diet and/or exercise alone 2) Alpha-glucosidase inhibitors in addition to diet and/or exercise 3) Thiazolidinedione in addition to diet and/or exercise 4) Sulfonylurea in addition to diet and/or exercise 5) Biguanides in addition to diet and/or exercise	25 January 2013	Marketing Authorisation
Japan	16 April 2010	Type 2 diabetes mellitus Patients with an insufficient response to: 1) Diet and/or exercise alone 2) Alpha-glucosidase inhibitors in addition to diet and/or exercise 3) Thiazolidinedione in addition to diet and/or exercise 4) Sulfonylurea in addition to diet and/or exercise 5) Biguanides in addition to diet and/or exercise	16 April 2010	Marketing Authorisation

08 ANALYSIS OF AVAILABLE DATA

The request for reimbursement of the VIPIDIA proprietary medicinal products is based on data from the phase III clinical studies performed in patients with type 2 diabetes mellitus, not achieving adequate glycaemic control and treated with alogliptin 12.5 and 25 mg:

- as monotherapy versus placebo: study 010;[10]
- as dual therapy with metformin in two studies versus:
  - the metformin/placebo combination: study 008,[11]
  - metformin/glipizide dual therapy: ENDURE study (305);
- as dual therapy with a sulfonylurea (glibenclamide) versus the glibenclamide/placebo combination: study 007;[12]
- in combination with insulin, with or without metformin versus placebo: study 011.[13]

The results of the EXAMINE safety study (402) were also provided, along with a follow-up study performed in patients included in the previously cited studies (OLE study 012).
All these studies, apart from study 010 as monotherapy, will be presented. In fact, the use of VIPIDIA as monotherapy does not form part of the MA.
The results of the two alogliptin dosages will be presented, namely the recommended daily dose of 25 mg and the recommended dose in case of moderate renal impairment, 12.5 mg.

08.1 Efficacy

8.1.1 Studies as dual therapy with metformin or a sulfonylurea versus placebo (008 and 007)

Studies 008 and 007 are two phase III, randomised, active-controlled, double-blind, parallel group and multicentre studies.[14]
The primary objective of these studies was to evaluate, in patients with type 2 diabetes mellitus, insufficiently controlled with monotherapy, the efficacy after 26 weeks of treatment with:

- dual therapy metformin/alogliptin, in the superiority study 008,
- dual therapy glibenclamide/alogliptin, in the superiority study 007.

The methods in these two studies are described in Table 1.

[10] DeFronzo RA, Fleck PR, Wilson CA, et al. Efficacy and Safety of the Dipeptidyl Peptidase-4 Inhibitor Alogliptin in Patients With Type 2 Diabetes and Inadequate Glycemic Control. Diabetes Care 2008. 31: 2315-7.
[11] Nauck,M, Ellis,G, Fleck,PR, Wilson,CA, Mekki,Q, Efficacy and safety of adding the dipeptidyl peptidase-4 inhibitor alogliptin to metformin therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a multicentre, randomised, double-blind, placebo-controlled study. Int J Clin Pract 2009. 63:46-55.
[12] Pratley,RE, Kipnes,MS, Fleck,PR, et al. Efficacy and Safety of the Dipeptidyl Peptidase-4 Inhibitor Alogliptin Added to Glyburide Therapy in Patients With Type 2 Diabetes Inadequately Controlled on Glyburide Monotherapy . Diabetes Obes Metab 2009. 11:167-76.
[13] Rosenstock,J, Rendell,M, Gross,J, et al. Alogliptin added to insulin therapy in patients with type 2 diabetes reduces HbA(1C) without causing weight gain or increased hypoglycaemia. Diabetes Obes Metab 2009. 11:1145-52.
[14] 169 centres in the DIA3006 study and 157 centres in the DIA3009 study, mainly in North, Central and South America and Europe.

Table 1. Methods of studies 008 and 007 evaluating alogliptin as dual therapy with an oral antidiabetic (OAD) versus placebo.

	Study 008: metformin/alogliptin vs metformin/placebo	Study 007: glibenclamide/alogliptin vs glibenclamide/placebo
Dates and sites	115 centres in 15 countries: USA, Brazil, Germany, New Zealand, UK, South Africa, Argentina, Australia, India, China, Holland, Hungary, Guatemala, Spain and Mexico. March 2006 to June 2007.	125 centres in 16 countries: USA, Mexico, Peru, Argentina, Brazil, Chile, Dominican Republic, Guatemala, Australia, New Zealand, Australia, Netherlands, UK, India, Poland, South Africa April 2006 to June 2007.
Inclusion criteria	- patients with type 2 diabetes mellitus aged between 18 and 80 years - HbA1c [7.0; 10.0] on antidiabetic treatment at a stable dose for at least 8 weeks: metformin ≥ 1.5 g/day (study 008) and glibenclamide 10 mg (study 007) - fasting C-peptide ≥ 0.8 ng/ml - BMI between 23 and 45 kg/m^2 - systolic blood pressure ≤ 180 mmHg and diastolic ≤ 110 mmHg - serum creatinine ≤ 1.5 mg/dl for men and ≤ 1.4 mg/dl for women in study 008 (on metformin) and ≤ 2.0 mg/dl in study 007 (on sulfonylurea)	
Main non-inclusion criteria	- urine albumin/creatinine > 1000 µg/mg - laser treatment for proliferative diabetic retinopathy during the previous 6 months - history of diabetic gastroparesis - congestive heart failure (NYHA class III or IV) or history of coronary angioplasty, stent, coronary bypass or myocardial infarction in the previous 6 months - history of angioedema in association with the use of an angiotensin-converting enzyme inhibitor or angiotensin II receptor inhibitor	
Exclusion criteria	Hyperglycaemia criteria requiring additional treatment: - from day 8 to the 4th week: fasting blood sugar (FBS) ≥ 275 mg/dl - from the 4th week to the 8th week FBS ≥ 250 mg/dl. - from the 8th week to the 12th week: FBS ≥ 225 mg/dl. - after the 12th week: HbA1c≥8.5% with reduction of ≤ 0.5% compared with baseline	
Administered treatments	After a period on metformin ≥ 1.5 g/day and placebo for 4 weeks, the patients were randomised* into three groups (randomisation* 2:2:1): - metformin/alogliptin 12.5 mg - metformin/alogliptin 25 mg - metformin/placebo The patients received the treatment for 26 weeks	After a period on glibenclamide ≥ 10 mg/day and placebo for 4 weeks, the patients were randomised* into three groups (randomisation* 2:2:1): - glibenclamide/alogliptin 12.5 mg - glibenclamide/alogliptin 25 mg - glibenclamide/placebo The patients received the treatment for 26 weeks
Primary efficacy endpoint	Change in HbA1c at 26 weeks	
Secondary endpoints included	Change at 26 weeks: - in the percentage of patients with an HbA1c level < 7.0% - in the weight - in the fasting blood sugar	
Statistical analysis	Difference between the alogliptin and placebo groups evaluated with an analysis of covariance (ANCOVA), adjusted for the dose of metformin/glibenclamide and the HbA1c value at inclusion. Hierarchical test procedure: if the test performed between the 25 mg dose and the placebo was significant (α=0.05), the test on the 12.5 mg dose was performed. Method for managing missing data: replacement with the last observation (LOCF analysis).	
Calculation of the number of subjects required (NSR)	Considering a change in HbA1c difference of 0.4% between the placebo and alogliptin with a standard deviation of 0.8%, the NSR was estimated at 500 to demonstrate the superiority of alogliptin with a power of 95% and alpha risk of 0.05.	

* stratified randomisation on HbA1c at 1 week (greater/equal or less than 8%) and geographical region

Study 008 results: metformin/alogliptin vs metformin/placebo

Treatment exposure

In study 008, 527 patients treated with metformin were randomised into three groups: alogliptin 12.5 mg (n=213), alogliptin 25 mg (n=207), placebo (n=104). The percentage of withdrawal or exclusion from the study was 16.9% in the alogliptin 12.5 mg group, 21.4% in the alogliptin 25 mg group and 30.7% in the placebo group; mainly due to the exclusion criteria (additional treatment required, see Table 1): 24.0% in the placebo group, 8.9% in the alogliptin 12.5 mg group and 8.1% in the alogliptin 25 mg group.

The mean dose of metformin at inclusion was 1847 mg (±468).

Patient characteristics

The patient characteristics were similar between the treatment groups. The patients had a mean age of 54.7 years (±10.6), 82.5% were aged less than 65 and 50.3% were men. Their mean weight was 88.7 kg (±19.5) with a mean BMI of 31.8 kg/m² (±5.4). The mean duration of type 2 diabetes mellitus was 6.1 years (±4.9). Amongst the included patients, 16.7% were obese, 53.5% had arterial hypertension and 21.6% had hyperlipidaemia. The mean HbA1c level was 8% at inclusion.

Efficacy with respect to the endpoints:

This study revealed the superiority of alogliptin, in combination with metformin, compared with the placebo at 26 weeks in terms of the change in HbA1c level, with an intergroup difference of -0.5 between each alogliptin group and the placebo (p<0.001). The per protocol population analysis confirms these results with an intergroup difference of -0.5 (p<0.001). It should be noted that the patients not having achieved the glycaemic target during the study and having been excluded were kept in the per protocol analysis. The LOCF method of data management was therefore applied in these patients.

In terms of secondary endpoints, the absolute responder rate (HbA1c ≤ 7.0%) and reduction of fasting blood sugar at 26 weeks was in favour of the alogliptin groups compared with the placebo group (Table 2). No difference in weight reduction was revealed between each of the alogliptin groups and the placebo group.

Table 2. Results of the analysis with respect to the primary and secondary efficacy endpoints in mITT at 26 weeks in study 008

	Placebo N=104	**Alogliptin 12.5 mg N=213**	**Alogliptin 25 mg N=207**	**Intergroup difference**	
				Alogliptin 12.5 mg - placebo	**Alogliptin 25 mg - placebo**
Primary efficacy endpoint					
HbA1c at inclusion (%), *mean (sd*)*	8.01 (0.87)	7.89 (0.74)	7.93 (0.80)	-	-
Change in HbA1c at 26 weeks, *mean (sd*)*	-0.10 (0.08)	-0.61 (0.05)	-0.59 (0.05)	-0.50 [-0.68; -0.32] p<0.001	-0.48 [-0.67;-0.30] p<0.001
Secondary endpoints					
Patients with HbA1c ≤ 7.0% at 26 weeks, n (%)	19 (18.3)	110 (51.6)	92 (44.4)	91 (33.3) p<0.001	73 (26.1) p<0.001
Fasting blood sugar (mmol/l), mean (sd) **At inclusion** **Change at 26 weeks**	 179.5 (50.3) 0.0 (3.6)	 168.3 (44.0) -18.7 (2.5)	 171.9 (45.7) -17.4 (2.5)	 -18.7 [-27.3; -10.2] p<0.001	 -17.4 [-25.9; -8.8] p<0.001
Weight (kg), mean (sd) **At inclusion** **Change at 26 weeks**	 89.3 (20.4) -0.4 (0.3)	 87.7 (18.4) -0.4 (0.2)	 88.1 (19.5) -0.7 (0.2)	 0.00 [-0.66; 0.66] p=0.99	 -0.28 [-0.94; 0.38] p=0.41

Study 007 results: glibenclamide/alogliptin vs glibenclamide/placebo

Treatment exposure

In study 007, 500 patients treated with glibenclamide were randomised into three groups: alogliptin 12.5 mg (n=203), alogliptin 25 mg (n=198), placebo (n=99). The percentage of withdrawal or exclusion from the study was 24.7% in the alogliptin 12.5 mg group, 25.3% in the alogliptin 25 mg group and 37.4% in the placebo group; mainly due to the exclusion criteria (additional treatment required, see Table 1): 28.3% in the placebo group, 14.8% in the alogliptin 12.5 mg group and 15.7% in the alogliptin 25 mg group.
The mean dose of glibenclamide at inclusion was 12.2 mg (±4.4).

Patient characteristics

The patient characteristics were similar between the treatment groups. The patients had a mean age of 56.6 years (±11.1), 74.0% were aged less than 65 and 56.6% were men. Their mean weight was 81.2 kg (±18.8) with a mean BMI of 30.1 kg/m² (±4.9). The mean duration of type 2 diabetes mellitus was 7.7 years (±5.9). Amongst the included patients, 11.2% were obese, 52.8% had arterial hypertension and 14.8% had hyperlipidaemia. The mean HbA1c was 8.1% at inclusion.

Efficacy with respect to the endpoints:

This study revealed the superiority of alogliptin, in combination with glibenclamide, compared with the placebo at 26 weeks in terms of the change in HbA1c level, with an intergroup difference of -0.4 between the alogliptin 12.5 mg group and the placebo group and -0.5 between the alogliptin 25 mg group and the placebo group (p<0.001). The per protocol population analysis confirms these results with an intergroup difference of -0.4 and -0.6 respectively (p<0.001). It should be noted that the patients not having achieved the glycaemic target during the study and having been excluded were kept in the per protocol analysis. The LOCF method of data management was therefore applied in these patients.

In terms of the secondary endpoints, the absolute responder rate (HbA1c≤7.0%) was in favour of the alogliptin 25 mg group compared with the placebo group at 26 weeks (Table 3). No difference in the fasting blood sugar was revealed between each of the alogliptin groups and the placebo group. The change in weight was in favour of the placebo.

Table 3. Results of the analysis with respect to the primary and secondary efficacy endpoints in mITT at 26 weeks in study 007

	Placebo N=99	**Alogliptin 12.5 mg N=203**	**Alogliptin 25 mg N=198**	**Intergroup difference**	
				Alogliptin 12.5 mg - placebo	**Alogliptin 25 mg - placebo**
Primary efficacy endpoint					
HbA1c at inclusion (%), *mean (sd*)*	8.15 (0.85)	8.08 (0.83)	8.09 (0.90)	-	-
Change in HbA1c at 26 weeks, *mean (sd*)*	+0.01 (0.08)	-0.38 (0.06)	-0.52 (0.06)	-0.39 [-0.59; -0.19] p<0.001	-0.53 [-0.73; -0.33] p<0.001
Secondary endpoints					
Patients with HbA1c≤7.0% at 26 weeks, n (%)	18 (18.2)	60 (29.6)	69 (34.8)	42 (11.4) p=0.057	51 (16.6) p=0.002
Fasting blood sugar (mmol/l), mean (sd) **At inclusion** **Change at 26 weeks**	 177.3 (52.2) 2.2 (4.8)	 171.9 (50.6) -4.7 (3.3)	 173.9 (48.8) -8.4 (3.4)	 -6.8 [-18.3; 4.6] p=0.241	 -10.5 [-22.0; 0.9] p=0.072
Weight (kg), mean (sd) **At inclusion** **Change at 26 weeks**	 80.8 (20.4) -0.2 (0.3)	 82.0 (17.5) +0.6 (0.2)	 80.4 (18.9) +0.7 (0.2)	 +0.8 [0.14; 1.46] p=0.018	 +0.88 [-0.94; 0.38] p=0.01

8.1.2 Study as dual therapy with metformin versus sulfonylurea (305 ENDURE)

The primary objective of study 305 was to evaluate the sustainability of alogliptin efficacy in combination with metformin compared with glipizide/metformin dual therapy in patients with type 2 diabetes mellitus, insufficiently controlled with monotherapy, at 52 and 104 weeks.
Only the results at 104 weeks will be presented.

Methods
Study 305 is a phase III, randomised, active-controlled, double-blind, multicentre study in parallel groups. This is a non-inferiority study.
The methods of this study are presented in Table 4.

Table 4. Methods of study 305 evaluating alogliptin in combination with metformin versus glipizide

	Study 305: metformin/alogliptin vs metformin/glipizide
Dates and sites	310 centres in 30 countries: North, Central and South America, Europe, Asia, Australia, New Zealand. March 2009 to October 2012.
Inclusion criteria	- patients with type 2 diabetes aged between 18 and 80 years - HbA1c [7.0; 9.0] and fasting blood sugar < 275 mg/dl despite treatment with a stable dose of metformin ≥ 1.5 g/day or after an 8-week stabilisation phase at a dose of ≥ 1.5 g/day for patients with HbA1c [7.5; 10.0] in pre-selection and initially on metformin < 1.5 g/day. - fasting C-peptide ≥ 0.8 ng/ml - BMI between 23 and 45 kg/m^2
Main non-inclusion criteria	- systolic blood pressure ≥ 150 mmHg and diastolic ≥ 90 mmHg - serum creatinine ≥ 1.5 mg/dl for men and 1.4 mg/dl for women and creatinine clearance < 60ml/min - laser treatment for proliferative diabetic retinopathy during the previous 6 months - history of diabetic gastroparesis, gastric bypass or gastric band - congestive heart failure (NYHA class III or IV) or history of coronary angioplasty, stent, coronary bypass or myocardial infarction, CVA or TIA in the previous 6 months - history of cancer, or basal cell or squamous cell carcinoma of the skin that has not been in full remission for at least 5 years - history or signs of thyroid disease
Exclusion criteria	Hyperglycaemia criteria requiring additional treatment: - from the 20th week to the 26th week: HbA1c ≥ 8.5% - from the 26th week to the 52nd week: HbA1c≥8.0% with a reduction of ≤ 0.5% compared with baseline - after the 52nd week: HbA1c≥7.5% with a reduction of ≤ 0.5% compared with baseline
Administered treatments	After a period on metformin and placebo for 4 weeks, the patients were randomised* into three groups (randomisation* 1:1:1): - metformin/alogliptin 12.5 mg - metformin/alogliptin 25 mg - metformin/glipizide 5 mg The patients received the treatment for 104 weeks.
Primary efficacy endpoints	Change in HbA1c: - at 52 weeks - at 104 weeks
Secondary endpoints included	Change at 104 weeks: - in the percentage of patients with an HbA1c level < 7.0% - in the weight - in the fasting blood sugar
Statistical analysis	Difference between the alogliptin and glipizide groups evaluated with ANCOVA, adjusted for the HbA1c value and the dose of metformin at inclusion. The non-inferiority analysis with a margin of 0.3% became superiority if the upper limit of the 98.75% CI of the difference was less than 0 (alpha risk = 0.0125). Missing data management method: LOCF analysis Hierarchical test procedure depending on the positive result of the tests: tests of non-inferiority then superiority for each of the two dosages.
Calculation of the number of subjects required (NSR)	By considering a change in HbA1c difference of 0.0% with a standard deviation of 1.2 between one of the alogliptin groups and the glipizide group, the NSR was estimated at 815 per group to demonstrate the non-inferiority of alogliptin (margin of 0.3%, alpha risk = 0.0125) with a power of 95%.

* stratified randomisation based on the HbA1c the week prior to randomisation (greater/equal or less than 8%), the country and whether or not a period of stabilisation was needed before inclusion.

Study 305 results: metformin/alogliptin vs metformin/glipizide

Treatment exposure

In study 305, 2638 patients treated with metformin were randomised into three groups: alogliptin 12.5 mg (n=880), alogliptin 25 mg (n=885), glipizide (n=873). The percentage of withdrawal or exclusion from the study at 104 weeks was 46.4% in the alogliptin 12.5 mg group, 44.3% in the alogliptin 25 mg group and 51% in the glipizide group; mainly due to the exclusion criteria (additional treatment required, see Table 4): 26.3% in the alogliptin 12.5 mg group, 22.7% in the alogliptin 25 mg group and 26.9% in the glipizide group.

During the study, the mean daily dose of metformin was 1829 mg (±390) and the mean daily dose of glipizide was 5.2 mg.

Patient characteristics

The patient characteristics were similar between the treatment groups. The patients had a mean age of 55.4 years (±9.7), 82.1% were aged less than 65 and 50.3% were women. Mean BMI was 31.2 kg/m² (±5.4). The mean duration of type 2 diabetes mellitus was 5.5 years (±5). Amongst the included patients, 18.2% were obese, 61% had arterial hypertension and 19.8% had hyperlipidaemia. The mean HbA1c level at inclusion was 7.6%.

Efficacy with respect to the endpoints at 104 weeks

This study revealed the non-inferiority of alogliptin, in combination with metformin, compared with glipizide at 104 weeks, in terms of HbA1c level change, with an upper limit of the 98.75% confidence interval of -0.04 for the difference between the 12.5 mg dose and glipizide and 0.01 for the difference between the 25 mg dose and glipizide, which is less than the non-inferiority margin of 0.30% (Table 5). This analysis was performed on the per protocol population of 1089 patients. In the ITT-LOCF population, the upper limit of the 98.75% confidence interval was less than 0[15] for the 25 mg dose (0.04) but above 0 for the observed case analysis. It should be noted that the interim analysis performed at 52 weeks revealed the non-inferiority of alogliptin with similar results.

In terms of secondary endpoints, the fasting blood sugar and weight change were in favour of the alogliptin groups at 104 weeks compared with glipizide; it was the same for the absolute responder rate (HbA1c≤7.0%) only for the 25 mg dosage (Table 5).

Table 5. Results of the analysis of the endpoints at 104 weeks in study 305

	Alogliptin 12.5 mg N=873	**Alogliptin 25 mg N=880**	**Glipizide N=885**	**Intergroup difference**	
				Alogliptin 12.5 - glipizide	**Alogliptin 25 - glipizide**
Primary efficacy endpoint (PP population)	**N=371**	**N=382**	**N=336**	**-**	**-**
HbA1c at inclusion (%), *mean (sd*)*	7.56 (0.52)	7.61 (0.53)	7.59 (0.53)	-	-
Change in HbA1c at 104 weeks, *mean (sd*)*	-0.68 (0.04)	-0.72 (0.04)	-0.59 (0.04)	-0.09 [-∞; -0.035]	-0.13 [-∞; 0.006]
Secondary endpoint (mITT population)	**N=873**	**N=878**	**N=869**	**-**	**-**
Patients with HbA1c≤7.0% at 104 weeks, n (%)	393 (45.6)	420 (48.5)	366 (42.8)	27 (2.8) p=0.250	54 (5.7) p=0.004
Fasting blood sugar (mmol/l), mean (sd) **At inclusion** **Change at 104 weeks**	 148.9 (34.2) -0.9 (1.3)	 149.5 (34.0) -3.2 (1.3)	 147.5 (33.4) 5.4 (1.3)	 -6.3 [-9.8; -2.7] p<0.001	 -8.6 [-12.1; -5.0] p<0.001
Weight (kg), mean (sd) **At inclusion** **Change at 104 weeks**	 85.4 (19.0) -0.7 (0.1)	 86.3 (19.4) -0.9 (0.1)	 85.5 (18.5) 1.0 (0.1)	 -1.63 [-1.986; -1.281]	 -1.84 [-2.191, -1.486]

[15] Threshold for the definition of alogliptin superiority.

	Alogliptin 12.5 mg N=873	Alogliptin 25 mg N=880	Glipizide N=885	Intergroup difference	
				Alogliptin 12.5 - glipizide	Alogliptin 25 - glipizide
				p<0.001	p<0.001

8.1.3 Study in combination with insulin (011)

The primary objective of study 011 was to evaluate the efficacy of alogliptin in combination with insulin compared with a placebo in patients with type 2 diabetes mellitus, insufficiently controlled with monotherapy and with or without metformin treatment.

Methods

Study 011 is a phase III, randomised, active-controlled, double-blind, multicentre study in parallel groups.

The methods of this study are similar to those of the two previous studies and are presented in Table 6.

Table 6. Methods of study 011 evaluating alogliptin in combination with insulin, with or without metformin, versus placebo

	Study 011: alogliptin/insulin +/- metformin vs placebo/insulin +/- metformin
Dates and sites	110 centres in 13 countries: USA, Mexico, Brazil, Chile, Guatemala, Australia, Germany, Netherlands, New Zealand, Hungary, India, Poland, South Africa. February 2006 to May 2007.
Inclusion criteria	- patients with type 2 diabetes mellitus aged between 18 and 80 years - HbA1c≥8.0% on insulin (between 15 and 100 IU/day) alone or in combination with metformin at a stable dose for at least 8 weeks - fasting C-peptide ≥ 0.8 ng/ml - BMI between 23 and 45 kg/m^2 - systolic blood pressure ≤ 180 mmHg and diastolic ≤ 110 mmHg
Main non-inclusion criteria	- urine albumin/creatinine > 1000 µg/mg - laser treatment for proliferative diabetic retinopathy during the previous 6 months - history of diabetic gastroparesis - congestive heart failure (NYHA) class III or IV) or history of coronary angioplasty, stent, coronary bypass or myocardial infarction in the previous 6 months - history of angioedema in association with the use of an angiotensin-converting enzyme inhibitor or angiotensin II receptor inhibitor - history of cancer, or basal cell or squamous cell carcinoma of the skin that has not been in full remission for at least 5 years
Exclusion criteria	Hyperglycaemia criteria requiring additional treatment: - from day 8 to the 4th week: fasting blood sugar (FBS) ≥ 300 mg/dl - from the 4th week to the 8th week FBS ≥ 275 mg/dl. - from the 8th week to the 12th week: FBS ≥ 250 mg/dl. - after the 12th week: HbA1c≥8.7% with reduction of ≤ 0.5% compared with baseline
Administered treatments	After a period on insulin +/- metformin and placebo for 4 weeks, the patients were randomised* into three groups (randomisation* 1:1:1): - insulin/alogliptin 12.5 mg +/- metformin - insulin/alogliptin 25 mg +/- metformin - insulin/placebo +/- metformin The patients received the treatment for 26 weeks
Primary efficacy endpoint	Change in HbA1c at 26 weeks
Secondary endpoints included	Change at 26 weeks: - in the percentage of patients with an HbA1c level < 7.0% - in the weight - in the fasting blood sugar
Statistical analysis	Difference between the alogliptin and placebo groups evaluated with an analysis of covariance (ANCOVA), adjusted for the region, the daily dose of insulin and the HbA1c value at inclusion. Hierarchical test procedure: if the test performed between the 25 mg dose and the placebo was significant (α=0.05), the test on the 12.5 mg dose was performed.
Calculation of the number of subjects	Considering a change in HbA1c difference of 0.4% between the placebo and alogliptin with a standard deviation of 0.8%, the NSR was estimated at 390 to demonstrate the superiority of alogliptin with a power of 94% and an alpha risk of 0.05.

	Study 011: alogliptin/insulin +/- metformin vs placebo/insulin +/- metformin
required (NSR)	

* stratified randomisation based on the HbA1c at 1 week (greater/equal or less than 9%), the geographical region and the treatment at inclusion (insulin alone or insulin/metformin)

Results

Treatment exposure

In study 011, 390 patients treated with insulin alone or combined with metformin were randomised into three groups: alogliptin 12.5 mg (n=131), alogliptin 25 mg (n=129), placebo (n=130). The percentage of withdrawal or exclusion from the study was 36.6% in the alogliptin 12.5 mg group, 40.3% in the alogliptin 25 mg group and 57.7% in the placebo group; mainly due to the exclusion criteria (additional treatment required, see Table 5): 40.0% in the placebo group, 20.6% in the alogliptin 12.5 mg group and 19.4% in the alogliptin 25 mg group.
The mean dose of insulin at inclusion was 56.9 IU/day (±22.9) and 56.3 IU/day at 26 weeks. The percentage of patients on insulin and metformin was 58.5%; the mean daily dose of metformin at inclusion was 1732.7 (±626.6). Therefore, 41.5% of patients were on insulin alone.

Patient characteristics

The patient characteristics were similar between the treatment groups. The patients had a mean age of 55.4 years (±10.2), 83.8% were aged less than 65 and 58.7% were women. Their mean weight was 88.6 kg (±20.1) with a mean BMI of 32.5 kg/m² (±5.6). The mean duration of type 2 diabetes mellitus was 12.6 years (±6.9). Amongst the included patients, 12.6% were obese, 69.5% had arterial hypertension and 20.5% had hyperlipidaemia. The mean HbA1c level at inclusion was 9.3%.

Efficacy with respect to the endpoints

This study revealed the superiority of alogliptin, in combination with insulin with or without metformin, compared with the placebo at 26 weeks, in terms of the change in HbA1c level, with an intergroup difference of -0.5 between the alogliptin 12.5 mg group and the placebo group and -0.6 between the alogliptin 25 mg group and the placebo group ($p<0.001$). The per protocol population analysis confirmed these results with an intergroup difference of -0.17 and -0.33 respectively ($p=0.009$ and $p<0.001$). It should be noted that the patients not having achieved the glycaemic target during the study and having been excluded were kept in the per protocol analysis. The LOCF method of data management was therefore applied in these patients.

The company provided a primary efficacy endpoint analysis in treatment subgroups (insulin alone or insulin/metformin). This analysis was not planned in the protocol. However, with the objective of effect evaluation in patients treated with metformin, the results are as follows in the subgroup of patients treated with insulin and metformin: the difference compared with the placebo group (n=79) was -0.5 [-0.8; -0.2] for the alogliptin 12.5 mg group (n=77) and -0.6 [0.9; -0.3] for the alogliptin 25 mg group (n=71).

In terms of the secondary endpoints, the absolute responder rate (HbA1c≤7.0%) at 26 weeks was in favour of the alogliptin 12.5 mg group compared with the placebo group; the fasting blood sugar change at 26 weeks was in favour of the 25 mg dosage. No difference for the weight change was found (Table 7).

Table 7. Results of the analysis with respect to the primary and secondary efficacy endpoints in mITT at 26 weeks in study 011

	Placebo N=130	Alogliptin 12.5 mg N=131	Alogliptin 25 mg N=129	Intergroup difference	
				Alogliptin 12.5 mg - placebo	Alogliptin 25 mg - placebo
Primary efficacy endpoint					
HbA1c at inclusion (%), *mean (sd*)*	9.28 (1.27)	9.29 (1.06)	9.27 (1.13)	-	-
Change in HbA1c at 26 weeks, *mean (sd*)*	-0.13 (0.08)	-0.63 (0.08)	-0.71 (0.08)	-0.51 [-0.72; -0.30] p<0.001	-0.59 [-0.80; -0.37] p<0.001
Secondary endpoints					
Patients with HbA1c≤7.0% at 26 weeks, n (%)	1 (0.8)	11 (8.4)	10 (7.8)	10 (7.6) p=0.048	9 (7.0) p=0.227
Fasting blood sugar (mmol/l), mean (sd) **At inclusion** **Change at 26 weeks**	196.0 (77.5) 5.8 (5.7)	189.8 (61.9) 2.3 (5.6)	186.3 (70.5) -11.7 (5.7)	-3.5 [-19.2; 12.2] p=0.662	-17.6 [-33.4;-1.7] p=0.030
Weight (kg), mean (sd) **At inclusion** **Change at 26 weeks**	91.9 (20.9) 0.6 (0.2)	88.2 (19.7) 0.7 (0.2)	85.8 (18.6) +0.6 (0.2)	+0.05 [-0.62; 0.72] p=0.87	-0.02 [-0.70; 0.65] p=0.95

08.2 Safety/Adverse effects

8.2.1 Data from the four main clinical studies

The adverse events from the four main clinical studies are presented in Table 8.
In total in these four studies, 1837 patients received at least one dose of alogliptin (919 of which at a dose of 25 mg).
The percentage of patients with adverse events varied between the studies and between groups. At 26 weeks, it was between 63 and 68% for the 12.5 mg dose of alogliptin, between 57 and 67% for the 25 mg dose and between 54 and 74% for the placebo. At 104 weeks, it was 79% for the 12.5 mg dose, 80 % for the 25 mg dose and 78% for glipizide. The majority of these events were of mild to moderate intensity. The most commonly reported adverse events (≥ 5.0%) in several studies were urinary tract infections, nasopharyngitis, diarrhoea and upper respiratory tract infections.
The percentage of patients with treatment-related adverse events varied from 11 to 15% for alogliptin 12.5 mg, 13 to 18% for alogliptin 25 mg and 10 to 12% for the placebo over 26 weeks. It was 25 and 26% for the alogliptin 12.5 mg and 25 mg doses respectively and 31% for glipizide at 104 weeks. These events were mainly hypoglycaemia, diarrhoea and nausea.

No difference was found compared with the placebo in terms of the percentages of patients with hypoglycaemia. However, this percentage was lower in study 305 compared with glipizide. In total, four patients had severe hypoglycaemia on alogliptin.

Serious adverse events were found in around 3 to 6% of patients on alogliptin over 26 weeks, and between 10 and 11% over 104 weeks, mainly cardiovascular and infection events, without any difference compared with the placebo. Between 6.8 and 8.4% of patients on alogliptin discontinued their treatment due to adverse events over the 104 weeks.
Eight deaths occurred in the alogliptin group compared with five in the glipizide group and one in the placebo group, mainly of cardiovascular origin. One of the deaths was possibly linked to treatment with alogliptin 25 mg in study 305 (acute pulmonary oedema).

Table 8. Adverse events found in the clinical studies

Studies	Dual therapy with metformin						Dual therapy with glibenclamide			In combination with insulin		
	Study 008 (26 weeks)			Study 305 (104 weeks)			Study 007 (26 weeks)			Study 011 (26 weeks)		
	Placebo N=104	Alogli 12.5 N=213	Alogli 25 N=210	Glipizide N=874	Alogli 12.5 N=880	Alogli 25 N=885	Placebo N=99	Alogli 12.5 N=203	Alogli 25 N=198	Placebo N=130	Alogli 12.5 N=131	Alogli 25 N=129
AE ≥ 3 %, *n (%)*	**69 (66.3)**	**134 (62.9)**	**118 (57.0)**	**676 (77.8)**	**689 (78.9)**	**701 (79.8)**	**53 (53.5)**	**129 (63.5)**	**125 (63.1)**	**95 (73.6)**	**89 (67.9)**	**86 (66.7)**
Diarrhoea	6 (5.8)	6 (2.8)	7 (3.4)	63 (7.2)	60 (6.9)	60 (6.8)	0	8 (3.9)	9 (4.5)	7 (5.4)	1 (0.8)	8 (6.2)
Nausea	*	*	*	21 (2.4)	28 (3.2)	32 (3.6)	*	*	*	3 (2.3)	4 (3.1)	6 (4.7)
Peripheral oedema	*	*	*	*	*	*	0	4 (2.0)	7 (3.5)	4 (3.1)	4 (3.1)	7 (5.4)
Nasopharyngitis	6 (5.8)	12 (5.6)	7 (3.4)	61 (7.0)	78 (8.9)	67 (7.6)	2 (2.0)	8 (3.9)	8 (4.0)	6 (4.7)	5 (3.8)	8 (6.2)
Urinary tract infection	4 (3.8)	14 (6.6)	6 (2.9)	39 (4.5)	42 (4.8)	34 (3.9)	3 (3.0)	9 (4.4)	10 (5.1)	10 (7.8)	8 (6.1)	9 (7.0)
Upper respiratory tract infection	7 (6.7)	10 (4.7)	5 (2.4)	76 (8.7)	84 (9.6)	90 (10.3)	6 (6.1)	4 (2.0)	5 (2.5)	4 (3.1)	6 (4.6)	4 (3.1)
Bronchitis	2 (1.9)	9 (4.2)	6 (2.9)	37 (4.3)	39 (7.5)	36 (4.1)	3 (3.0)	3 (1.5)	1 (0.5)	4 (3.1)	3 (2.3)	1 (0.8)
Arthralgia	5 (4.8)	4 (1.9)	3 (1.4)	40 (4.6)	39 (4.5)	42 (4.8)	*	*	*	3 (2.3)	9 (6.9)	4 (3.1)
Lumbar pain	*	*	*	*	*	*	3 (3.0)	4 (2.0)	9 (4.5)	2 (1.6)	2 (1.5)	6 (4.7)
Headaches	2 (1.9)	8 (3.8)	4 (1.9)	46 (5.3)	46 (5.3)	61 (6.9)	3 (3.0)	5 (2.5)	11 (5.6)	6 (4.7)	7 (5.3)	4 (3.1)
Hypertension	5 (4.8)	4 (1.9)	6 (2.9)	65 (7.5)	46 (5.3)	68 (7.7)	2 (2.0)	7 (3.4)	11 (5.6)	*	*	*
Hypoglycaemia	**3 (2.9)**	**2 (0.9)**	**0**	**202 (23.2)**	**22 (2.3)**	**12 (1.4)**	**11 (11.1)**	**32 (15.5)**	**19 (9.6)**	**31 (24.0)**	**35 (26.7)**	**35 (27.1)**
- severe	**0**	**0**	**0**	**5 (0.6)**	**0**	**1 (0.1)**	**1 (1.0)**	**2 (1.0)**	**0**	**2 (1.6)**	**0**	**1 (0.8)**
Treatment-related AE, *n (%)*	**10 (9.6)**	**24 (11.3)**	**26 (12.6)**	**271 (31.2)**	**219 (25.1)**	**231 (26.3)**	**10 (10.1)**	**31 (15.3)**	**35 (17.7)**	**16 (12.4)**	**14 (10.7)**	**17 (13.2)**
Diarrhoea	0	4 (2.0)	4 (2.0)	22 (2.5)	23 (2.6)	25 (2.8)	0	1 (0.5)	1 (0.5)	3 (2.3)	1 (0.8)	1 (0.8)
Nausea	1 (1.0)	0	3 (1.5)	13 (1.5)	15 (1.7)	22 (2.5)	1 (1.0)	0	3 (1.5)	0	1 (0.8)	4 (3.1)
Serious AE, *n (%)*	**4 (3.8)**	**6 (2.8)**	**8 (3.9)**	**81 (9.3)**	**86 (9.9)**	**97 (11.0)**	**2 (2.0)**	**11 (5.4)**	**11 (5.6)**	**6 (4.7)**	**8 (6.1)**	**7 (5.4)**
Cardiovascular	1 (1.0)	2 (1.0)	2 (1.0)	21 (2.4)	14 (1.6)	23 (2.6)	0	3 (1.5)	2 (1.0)	1 (0.8)	4 (3.1)	1 (0.8)
Infections	2 (2.0)	0	1 (0.5)	18 (2.1)	11 (1.3)	14 (1.6)	2 (2.0)	2 (2.0)	2 (2.0)	0	1 (0.8)	2 (1.6)
Neoplasia	0	3 (1.5)	0	4 (0.5)	9 (1.0)	11 (1.3)	0	0	2 (1.0)	1 (0.8)	0	0
Treatment-related SAE, *n (%)*	**0**	**0**	**2 (1.0)**	**10 (1.2)**	**11 (1.3)**	**12 (1.4)**	**1 (1.0)**	**1 (0.5)**	**0**	**0**	**1 (0.8)**	**0**
Discontinuation linked to AE, n (%)	**1 (1.0)**	**7 (3.3)**	**4 (1.9)**	**82 (9.4)**	**59 (6.8)**	**74 (8.4)**	**2 (2.0)**	**5 (2.5)**	**4 (2.0)**	**4 (3.1)**	**1 (0.8)**	**6 (4.7)**
Death, *n*	**0**	**1 (0.5)**	**0**	**5 (0.6)**	**3 (0.3)**	**3 (0.3)**	**0**	**0**	**0**	**0**	**1 (0.8)**	**0**

*< 3%

8.2.2 EXAMINE study

Methods

The EXAMINE study is a phase IIIb, randomised, placebo-controlled, multicentre, double-blind study in parallel groups. The primary objective of this study was to evaluate the cardiovascular safety of alogliptin compared with a placebo in patients with type 2 diabetes mellitus, insufficiently controlled with antidiabetics and having a history of acute coronary syndrome during the 15 to 90 days prior to randomisation (myocardial infarction or unstable angina requiring hospitalisation).
The patients with an HbA1c level between 6.5 and 11.0% on oral antidiabetic treatment (between 7.0 and 11.0% on insulin treatment) were included and treated for a maximum duration of 4.5 years. The patients treated with gliptins or GLP-1 analogues, or with an unstable cardiac disease (NYHA class III or IV congestive heart failure, refractory angina, uncontrolled arrhythmia, valve disease, severe uncontrolled hypertension) or having had a CVA during the 15 previous days were not included.

The primary endpoint was a composite endpoint, namely the time to occurrence of the first major cardiovascular event (MACE): cardiovascular death, non-fatal myocardial infarction (MI) and stroke (CVA).
The secondary efficacy endpoint, also a composite endpoint, corresponded to the addition of unstable angina (requiring emergency revascularisation) to the previous cardiovascular events which make up primary efficacy endpoint.
The primary efficacy endpoint was analysed with a Cox proportional hazard model, stratified according to the region and renal function at inclusion. The difference between the groups was evaluated with a non-inferiority analysis with a margin of 1.3. The number of subjects required was estimated at 5400 patients (one-sided alpha of 0.025) with a power of 91%.

Results

A total of 5380 patients were randomised into two groups: alogliptin (n=2701), placebo (n=2679). The percentage of withdrawals from the study was 22.6% in the alogliptin group and 20.9% in the placebo group, mainly due to adverse events (10% on average).

The patient characteristics were similar between the treatment groups. The patients had a mean age of 60.9 years (±9.9), and 67.9% were men. The mean BMI was 29.5 kg/m² (±5.6). The mean duration of type 2 diabetes mellitus was 9.2 years (±8.2) and the HbA1c level was 8%. Amongst the included patients, 77.2% had had a myocardial infarction during the pre-selection period and 22.6% had had unstable angina. The majority of these patients had arterial hypertension (88%) and 73% were at least on metformin.

Endpoints

A total of 621 patients had a cardiovascular event from the primary endpoint. The rate of occurrence was 11.3% in the alogliptin group versus 11.8% in the placebo group after a mean follow-up of 19 months (HR: 0.96 [0; 1.16]); marking the non-inferiority of alogliptin compared with the placebo (Table 8).
Similar results were found for the secondary efficacy endpoint.

Table 8. Results for the primary efficacy endpoint from the EXAMINE study

	Placebo n=2679	Alogliptin n=2701
Number of patients with a cardiovascular event, n (%)	316 (11.8)	305 (11.3)
CV death	111 (4.1)	89 (3.3)
Non-fatal MI	173 (6.5)	187 (6.9)
Non-fatal CVA	32 (1.2)	29 (1.1)
Hazard ratio (alogliptin vs placebo)		0.962
Confidence Interval.		[0; 1.16]

The assessment of the change in HbA1c level forms part of the exploratory endpoints; it will therefore not be presented, especially since the oral antidiabetic treatments were intensified during the study.

Other adverse events

In total, 2698 patients received at least one dose of alogliptin. The duration of treatment was 17 months. The percentage of patients with adverse events was 79.4% without any difference between the placebo and alogliptin groups.

In the alogliptin group, this was mainly:

- impaired renal function (7.7 versus 6.7% in the placebo group),
- Arterial hypertension (7.3 versus 7.8%)
- hypoglycaemia (6.7 versus 6.5%, of which severe hypoglycaemia: 0.7 versus 0.3% respectively),
- increased CPK (5.2 versus 4.3%).

These adverse events were treatment-related for 18.5% of the patients in the alogliptin group.

The adverse events were responsible for treatment discontinuation for 10% of patients with no difference between the two groups.

The percentage of serious adverse events was 33.6 % in the alogliptin group and 35.5 % in the placebo group, mainly cardiovascular. They were treatment-related for 1.3% of patients in each group.

It should be noted that acute pancreatitis was observed in 0.7% of patients in the alogliptin group without difference compared with the placebo (0.6%).

Mortality rates were 5.7% in the alogliptin group and 6.5% in the placebo group. The majority of these deaths were of cardiovascular origin.

8.2.3 Study OLE-012

Study OLE-012 is a follow-up, open-label study performed in patients having completed or withdrawn early (due to hyperglycaemia) from one of the seven studies provided in the registration file, including the four phase III studies described previously.

This study included 3323 patients. Of the 3320 patients having received at least one dose of alogliptin, 86.7% had at least one adverse event. It should be noted that 13 patients had pancreatitis, 4 of which were attributed to the treatment and 1 led to death. The consideration of the safety results of this study is limited given its open-label and non-comparative design.

8.2.4 SPC data

"In the pooled pivotal phase 3 controlled clinical trials of alogliptin as monotherapy and as add-on combination therapy involving 5658 patients, the observed adverse reactions are listed below."

The adverse effects reported according to their frequency were:

- Common (in the clinical studies): upper respiratory tract infection, nasopharyngitis, headaches, abdominal pains, gastro-oesophageal reflux, pruritus and rash;
- Undetermined frequency (spontaneously reported post-marketing): hypersensitivity, acute pancreatitis, hepatic dysfunction including hepatic failure, skin disorders (exfoliative lesions including Stevens-Johnson), angioedema, urticaria.

08.3 Summary and discussion

The request for inclusion of VIPIDIA in combination with other antidiabetics is based on the data from four phase III, randomised, controlled, multicentre, double-blind studies performed in type 2 diabetic patients, insufficiently controlled with an antidiabetic treatment, and a cardiovascular safety study.
The primary efficacy endpoint used in the four phase III studies was the change in HbA1c over the predefined periods.

Studies as dual therapy in combination with metformin
Two studies evaluated alogliptin in combination with metformin, one versus placebo (study 008) and the other versus a sulfonylurea, glipizide, via a non-inferiority study (study 305).

Study 008 included 527 patients with a mean age of 55 years with type 2 diabetes for almost 6 years, and a mean HbA1c level at inclusion of 7.9%. These patients were randomised into three groups according to a 2:2:1 design (alogliptin 12.5 mg, alogliptin 25 mg, placebo).
According to the methodology of the study, at 26 weeks this study revealed the superiority of alogliptin 12.5 mg and 25 mg compared with the placebo, in terms of HbA1c change with an intergroup difference compared with the placebo of 0.50 (95% CI: [-0.7; -0.3]) for each of the alogliptin dosages.
Amongst the secondary endpoints at 26 weeks, the responder rate was in favour of alogliptin 12.5 and 25 mg compared with the placebo with 51.6 and 44.4% responders respectively (HbA1c<7/0%) versus 18.3%.

Study 305 included 2638 patients with a mean age of 55 years with type 2 diabetes for almost 6 years, and a mean HbA1c level at inclusion of 7.6%. These patients were randomised into three groups: alogliptin 12.5 mg, alogliptin 25 mg, glipizide.
This study revealed the non-inferiority of alogliptin 12.5 and 25 mg at 104 weeks compared with glipizide in terms of HbA1c change with an intergroup difference compared with the glipizide group of -0.09 (95% CI: [-∞; -0.04]) for alogliptin 12.5 mg and -0.13 (95% CI: [∞; -0.01]) for alogliptin 25 mg, complying with the upper limit of non-inferiority for the 98.75% confidence interval fixed at 0.30. This analysis was performed on the per protocol population of 1,089 patients, after exclusion of more than 50% of patients, mainly for not achieving the glycaemic targets regularly fixed during the study. In the ITT-LOCF population, the upper limit of the 98.75% confidence interval was less than 0 (superiority definition threshold) for the 25 mg dose (0.04) but above 0 for the observed case analysis.
Of the secondary endpoints, only alogliptin 25 mg was superior to glipizide at 52 weeks in terms of the responder rate (HbA1c<7.0%) with 48.5% versus 42.8% of patients respectively.

In total, these studies revealed the superiority of alogliptin 12.5 and 25 mg compared with the placebo in combination with metformin at doses ≥ 1500 mg/day (< 2000 mg/day) and the non-inferiority of the two dosages compared with glipizide (sulfonylurea) by setting a non-inferiority limit of 0.30% in accordance with the recommendations. According to the methodology, the exclusion of patients based on not achieving the glycaemia reduction criteria during the non-inferiority study resulted in selection of responder patients which could overestimate the effect of the substance.
In these two studies, the reduction of HbA1c between inclusion and 26 or 104 weeks was 0.6 and 0.7% for alogliptin, from a moderately elevated mean HbA1c level at inclusion (7.6% and 7.9%). The difference in the responder rate compared with the placebo was low with 33% and 26% for the 12.5 and 25 mg dosages respectively at 26 weeks and it was 3 and 6% with glipizide at 52 weeks.
It should be noted that there was little difference in terms of efficacy on HbA1c revealed for the two dosages.

Study as dual therapy in combination with a sulfonylurea

Study 007 evaluated alogliptin in combination with glibenclamide versus a placebo.

This study included 500 patients with a mean age of 57 years with type 2 diabetes mellitus for almost 8 years, and a mean HbA1c level at inclusion of 8.1%. These patients were randomised into three groups: alogliptin 12.5 mg, alogliptin 25 mg, placebo.

At 26 weeks, this study revealed the superiority of alogliptin 12.5 mg and 25 mg compared with the placebo, in terms of HbA1c change, with an intergroup difference compared with the placebo of -0.4 (95% CI: [-0.6; -0.2]) for alogliptin 12.5 mg and -0.5 (95% CI: [-0.7; -0.3]) for alogliptin 25 mg.

Of the secondary endpoints, only alogliptin 25 mg was superior to the placebo in terms of the responder rate (HbA1c<7.0%) with 34.8% versus 18.2% of responders. A weight gain was observed in the alogliptin groups (0.6 to 0.7 kg) which was not the case in the placebo group.

This study revealed the superiority of alogliptin in combination with glibenclamide compared with the placebo. The change in HbA1c with alogliptin as dual therapy, compared with baseline was -0.4% for the 12.5 mg dose and -0.5% for the 25 mg dose at 26 weeks from an HbA1c value of 8.1%. The difference in the responder rate compared with the placebo was low with 16.6% for the 25 mg dosage and this percentage was not different with the placebo for the 12.5 mg dosage. A low efficacy difference between the two dosages was also revealed in these two studies.

Study in combination with insulin

Study 011 evaluated alogliptin in combination with insulin alone or in combination with metformin versus a placebo.

This study included 390 patients with a mean age of 55 years with type 2 diabetes for almost 13 years, and a mean HbA1c level at inclusion of 9.3%. These patients were randomised into three groups: alogliptin 12.5 mg, alogliptin 25 mg, placebo. The percentage of patients on insulin and metformin was 58.7%.

At 26 weeks, this study revealed the superiority of alogliptin 12.5 mg and 25 mg compared with the placebo, in terms of HbA1c change, with an intergroup difference with the placebo of -0.5 (95% CI: [-0.7; -0.3]) for alogliptin 12.5 mg and -0.6 (95% CI: [-0.8;-0.4]) for alogliptin 25 mg.

Of the secondary endpoints, only alogliptin 12.5 mg was superior to the placebo in terms of the responder rate (HbA1c<7%) with 7.6% of responders versus 0.8%.

This study revealed the superiority of alogliptin in combination with insulin +/- metformin compared with the placebo. However, 58.5% of patients were not treated with insulin alone in a low number of included patients. Therefore, the transposability of the results to patients treated with insulin alone is not known. As a reminder, these substances are not recommended in combination with insulin alone. The analysis of the insulin alone or in combination with metformin subgroups which revealed similar results was not planned in the protocol. However, with the objective of an evaluation of alogliptin administration in combination with metformin and insulin, these results are considered.

The change in HbA1c with alogliptin, compared with baseline was -0.6% for the 12.5 mg dose and -0.7% for the 25 mg dose at 26 weeks from an HbA1c value of 9.3%. The responder rate (HbA1c<7.0%) was therefore low with a difference of 7.6% compared with the placebo.

Safety

At 26 weeks, the percentage of patients with adverse events was between 63 and 68% for the 12.5 mg dose of alogliptin, between 57 and 67% for the 25 mg dose and between 54 and 74% for the placebo. At 104 weeks, it was 79% for the 12.5 mg dose, 80% for the 25 mg dose and 78% for glipizide. The majority were of mild to moderate intensity. The most commonly reported treatment-related adverse events were hypoglycaemia, diarrhoea and nausea. The serious adverse events involved between 2 and 6% of patients over 26 weeks, mainly cardiovascular and infection events, and between 10 and 11% of patients on sulfonylurea over 104 weeks, of which 1% were treatment-related.

In the EXAMINE study, having evaluated the cardiovascular safety over a median duration of 19 months, no difference was revealed in terms of occurrence of major cardiovascular events

compared with the placebo. Acute pancreatitis was reported in 0.7% of patients treated with alogliptin and 0.6% of patients in the placebo group.

08.4 Planned studies

A risk management plan (RMP) is envisaged to monitor certain aspects relating to safety of use. The risks monitored are:

- Significant identified risks: hypersensitivity reactions, pancreatitis;
- Significant potential risks: hepatotoxicity, necrotic peripheral skin lesions, gastrointestinal disorders, infections, pancreatic cancer;
- Missing information: patients with cardiovascular disease or severe renal impairment or end-stage renal disease requiring dialysis, pregnant or breastfeeding women, children and adolescents, tumours.

09 THERAPEUTIC USE

The objective of treatment in type 2 diabetes mellitus is to reduce morbidity and mortality, in particular through correct glycaemic control. According to the HAS guidelines in 2013,[4] the glycaemic target of patients with type 2 diabetes mellitus is to be defined for each patient depending on comorbidities and life expectancy: the HbA1c target varies between 6.5% and 8%. A target HbA1c less than or equal to 7% is recommended for the majority of patients. The drug treatment should be initiated or re-assessed if the HbA1c is higher than 7%.

<u>As monotherapy</u>
According to the HAS guidelines, if the glycaemic target is not achieved despite the implementation of lifestyle and dietary measures, monotherapy must be started with metformin as first-line treatment or, in case of contraindications, sulfonylureas (if these two substances are contraindicated, repaglinide or alpha-glucosidase inhibitors are recommended).

<u>Dual therapy with oral antidiabetics</u>
If the glycaemic target is not achieved with monotherapy, dual therapy is recommended combining metformin and sulfonylureas as first-line treatment, while monitoring the weight and occurrence of hypoglycaemia. In the case of contraindication or intolerance to sulfonylureas,[16] metformin can be combined with alpha-glucosidase inhibitors, repaglinide or DPP-4 inhibitors (gliptins).
In case of intolerance or contraindication to metformin, sulfonylureas can be used, in combination with alpha-glucosidase inhibitors and gliptins.
Given the results from the clinical trials, alogliptin, the fifth drug in the gliptin class, forms part of the therapeutic alternatives in these two indications, alongside the other gliptins.

The use of GLP-1 analogues is possible at the dual therapy stage if the BMI is greater than or equal to 30 kg/m^2 or if the increase in weight on insulin or the occurrence of hypoglycaemia are of concern.

<u>Triple therapy with oral antidiabetics</u>
If the glycaemic target is not achieved despite dual therapy with metformin + sulfonylurea, an alpha-glucosidase inhibitor or a gliptin can be added.
In the absence of efficacy data, the use of alogliptin as triple therapy with metformin and a sulfonylurea is not recommended.

[16] if the difference from the target is less than 1% for HbA1c

In combination with insulin therapy

The benefit of maintaining oral antidiabetics should be assessed depending on the expected benefits for each of the substances. Therefore, where appropriate, metformin or sulfonylureas (after dosage adjustment) could be continued.[17,18,19]

In the clinical studies provided, alogliptin was evaluated without distinction in combination with insulin alone or with oral antidiabetics. Given the transposability difficulties of these results with respect to patients on dual therapy with insulin, and due to the fact that the validated dual therapy combinations are insulin/metformin and insulin/sulfonylurea, alogliptin cannot be recommended as dual therapy with insulin.

However, it constitutes an additional method as triple therapy in combination with 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.

The Committee notes that little difference in efficacy in terms of HbA1c change was revealed between the 12.5 mg dosage and that of the 25 mg dosage, which is recommended in the SPC.

Diabetes mellitus is progressive and treatment should be regularly re-assessed in all its components: lifestyle and dietary measures, therapeutic education and drug treatment.

[17] Hemmingsen B, Christensen LL, Wetterslev J, Vaag A, Gluud C, Lund SS, Almdal T. Comparison of metformin and insulin versus insulin alone for type 2 diabetes: systematic review of randomised clinical trials with meta-analyses and trial sequential analyses. BMJ. 2012 Apr 19; 344: e1771. doi: 10.1136/bmj.e1771.

[18] Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, 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.*

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

010 TRANSPARENCY COMMITTEE CONCLUSIONS

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

010.1 Actual benefit

◗ Type 2 diabetes mellitus is a chronic disease with potentially serious complications, particularly cardiovascular complications.
◗ These proprietary medicinal products are intended as the symptomatic therapy of glycaemia in type 2 diabetes mellitus.
◗ The efficacy/adverse effects ratio is:

- Substantial as dual therapy in combination with metformin or a sulfonylurea.
- Moderate as triple therapy with metformin and insulin given the methodological weaknesses.
- Non-quantifiable:
  - as triple therapy with metformin and a sulfonylurea due to the absence of data,
  - as dual therapy with insulin given the transposability difficulties of the study results with a low proportion of patients treated with dual therapy and the absence of recommendations other than metformin and sulfonylurea.

◗ Alogliptin is an supplementary therapeutic agent in insufficiently controlled type 2 diabetes mellitus:

- as dual therapy in combination with metformin, from the available oral antidiabetics, in case of intolerance or contraindication to sulfonylureas,
- as dual therapy in combination with a sulfonylurea, from the available oral antidiabetics, in case of intolerance or contraindication to metformin,
- as triple therapy in combination with metformin and insulin.

In the absence of data, alogliptin cannot be recommended as triple therapy with metformin and a sulfonylurea.
Given the transposability difficulties and the absence of guidelines, alogliptin can no longer be recommended as dual therapy with insulin.
◗ There are treatment alternatives to this proprietary medicinal product.

◗ Public health benefit:
Due to its elevated prevalence which is constantly increasing, and the associated microvascular and macrovascular complications, the public health burden of type 2 diabetes mellitus is substantial. The public health burden in the subpopulation of patients for each of the VIPIDIA indications is considered to be moderate.
Improving the therapeutic management of patients with type 2 diabetes mellitus is a public health need which is an established priority (Objective 55 of the Law of 9 August 2004 on public health policy, National plan to improve the quality of life of patients with chronic diseases 2007-2011). Access to effective treatments which are well tolerated in type 2 diabetic patients is a public health need.
In view of the results of the clinical studies performed in all the indications, no additional impact on glycaemic control is expected from the proprietary medicinal product VIPIDIA. Data from the "Examine" cardiovascular safety study performed in patients with a recent history of acute coronary syndrome, make it difficult to estimate the impact of VIPIDIA on the morbidity-mortality given the duration of follow-up in the study. In addition, the available data do not enable the impact on the quality of life of patients with type 2 diabetes mellitus to be estimated compared with currently available treatments, and due to the safety problems, a negative impact of VIPIDIA cannot be excluded.
VIPIDIA is not expected to have any impact on the organisation of healthcare.

In addition, it is not certain that it will be possible to transpose the experimental data into clinical practice because of uncertainties about the long-term effect of this treatment on glycaemic control.
In the current state of knowledge, the proprietary medicinal product VIPIDIA offers a partial response to an identified public health need.
It is therefore not expected that the proprietary medicinal product VIPIDIA will impact public health in all the Marketing Authorisation indications.

Taking account of these points, the Committee considers that the actual benefit of VIPIDIA is:

- **substantial as dual therapy in combination with metformin,**
- **substantial as dual therapy in combination with a sulfonylurea,**
- **insufficient as dual therapy in combination with insulin,**
- **insufficient as triple therapy in combination with metformin and a sulfonylurea,**
- **moderate as triple therapy in combination with metformin and insulin.**

010.2 Improvement in actual benefit

<u>In the indications as dual therapy in combination with metformin or a sulfonylurea and as triple therapy in combination with metformin and insulin:</u>
Given the absence of demonstrated superiority compared with available oral antidiabetics, and in the absence of data on the long-term safety, the Committee considers that the VIPIDIA proprietary medicinal products do not provide any improvement in actual benefit (level V, non-existent) in the management of patients with insufficiently controlled type 2 diabetes mellitus as dual oral therapy in combination with metformin or a sulfonylurea, and as triple therapy in combination with metformin and insulin.

<u>In the indications as dual therapy in combination with insulin and as triple therapy in combination with metformin and a sulfonylurea:</u>
Not applicable.

010.3 Target population

In 2012, the EGB [General sample of beneficiaries] identified 26,308 patients with type 2 diabetes mellitus, which is 2,943,147 after extrapolation to France. According to the ENTRED 2007-2010 study, 91.9% of diabetic patients have type 2 diabetes mellitus. Therefore, the number of patients with type 2 diabetes mellitus in France would be 2,714,292.

The number of patients treated with metformin monotherapy would be: 702,905, amongst which 8% would present hypoglycaemia on sulfonylurea (HAS study 2006), which would represent intolerance, which is 56,232 patients.

The guidelines position the role of sulfonylureas as monotherapy in the case of intolerance or contraindication to metformin. In a previous opinion, the Committee assessed that 20% of the patients would be affected by contraindication or intolerance to metformin.

According to the estimation of 702,905 patients treated with metformin, we can therefore assume that almost 140,581 patients would be treated with sulfonylurea monotherapy due to contraindication or intolerance to metformin. The ENTRED 2007-2010 study indicates that 50% of these patients would not be at the target, which is 70,291 patients.

As triple therapy, in combination with insulin and metformin, the target population of VIPIDIA in this indication was recently assessed by the Committee for another DPP-4 inhibitor and estimated as 113,000 people.[20]

Overall, the target population of VIPIDIA would be 239,523 patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

In the indications as dual therapy in combination with metformin or a sulfonylurea, and as triple therapy in combination with metformin and insulin:
The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use at the dosages in the Marketing Authorisation.

◗ Proposed reimbursement rate: 65%

In the indications as dual therapy in combination with insulin, and as triple therapy in combination with metformin and a sulfonylurea:
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 at the dosages in the Marketing Authorisation.

◗ Packaging

It is not appropriate for the prescribing conditions. Packaging in boxes of 30, 60 or 90 tablets would be more appropriate.

[20] Transparency Committee Opinion. TRAJENTA 5 mg. 20 March 2013.

APPENDIX

INN	Name (Company)	Date of opinion	AB	IAB	Reimbursement
Biguanide					
Metformin and its generics	GLUCOPHAGE (Merck Santé)	21 July 2010 (RI)	Substantial		Yes
Insulin secretagogues					
Sulfonylureas and their generics			Substantial		Yes
Alpha-glucosidase inhibitors (acarbose, miglitol)	GLUCOR (Bayer Santé) DIASTABOL (Sanofi Aventis)	5 September 2012 (RI)	Substantial		Yes
Repaglinide	NOVONORM (Novo Nordisk)	21 July 2010 (RI)	Substantial		Yes
Injectable incretin mimetic or GLP-1 analogues (not indicated as monotherapy)					
Exenatide	BYETTA (Bristol-Myers Squibb)	28 February 2007	Substantial as dual therapy in combination with metformin or a sulfonylurea	V	Yes
			Being assessed as dual therapy and as triple therapy + metformin		
Liraglutide	VICTOZA (Novo Nordisk)	2 December 2009	Substantial as dual therapy in combination with metformin or a sulfonylurea	IV	Yes
Lixisenatide	LYXUMIA (Sanofi Aventis)	*Still being assessed by the TC*			
Gliptins					
Sitagliptin and its fixed combinations with metformin	JANUVIA 100 mg/XELEVIA 100 mg (MSD, Pierre Fabre)	18 July 2012	Insufficient as monotherapy	-	
		6 June 2007	Substantial as dual therapy in combination with metformin	IV	Yes
		24 June 2009	low as dual therapy in combination with a sulfonylurea	V	Yes
		18 July 2012	Insufficient as dual therapy in combination with insulin	-	No
		18 July 2012	Substantial as triple therapy in combination with insulin and metformin	V	Yes
Vildagliptin and its fixed-dose	GALVUS/JALRA	21 Nov. 2012	Insufficient as monotherapy	-	

INN	Name (Company)	Date of opinion	AB	IAB	Reimbursement
combinations with metformin	(Novartis Pharma)[21]	10 December 2008	substantial as dual therapy in combination with metformin or a sulfonylurea	V	Yes
Saxagliptin and its fixed combination with metformin	ONGLYZA (Bristol-Myers Squibb)[22]	2 December 2009	Substantial as dual therapy in combination with metformin or a sulfonylurea	V	Yes
		15 May 2013	Insufficient as dual therapy in combination with insulin	-	No
			Low as triple therapy in combination with insulin and metformin	V	Yes
Linagliptin and its fixed-dose combination	TRAJENTA (Boehringer Ingelheim)[23]	20 June 2012	Insufficient as monotherapy	-	No
			Substantial as dual therapy in combination with metformin	V	
		20 March 2013	Insufficient as dual therapy in combination with insulin	-	
			Substantial as triple therapy in combination with insulin and metformin	V	
Sodium/Glucose cotransporter 2 inhibitors					
Dapagliflozin	FORXIGA	23 April 2014	Insufficient as monotherapy	-	No
			Moderate as dual therapy in combination with metformin or a sulfonylurea	V	
			Insufficient as dual therapy in combination with insulin		
			Moderate as triple therapy in combination with insulin and metformin	V	

[21] On 20 September 2012, vildagliptin-based proprietary medicinal products received a favourable opinion from the CHMP in the following extension of indication: “in combination with insulin, with or without metformin, when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control. "
[22] Not indicated as monotherapy
[23] Not indicated as dual therapy in combination with a sulfonylurea