HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

20 March 2013

TRAJENTA 5 mg, film-coated tablets

B/30 (CIP: 34 009 217 743-5 1)

Applicant: BOEHRINGER INGELHEIM FRANCE

INN	Linagliptin
ATC code (2013)	A10BH05 (DPP-4 inhibitor or gliptin)
Reason for the review	**Inclusion for an extension of the indication**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indication concerned	"TRAJENTA is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults **in combination with insulin with or without metformin**, when this regimen alone, with diet and exercise, does not provide adequate glycaemic control."

Actual Benefit	Insufficient in dual therapy, in addition to insulin when this regimen alone, with diet and exercise, does not provide adequate glycaemic control, for reimbursement by National Health Insurance. Substantial in triple therapy, in combination with insulin and metformin when this combination alone, with diet and exercise, does not provide adequate glycaemic control.
Improvement in Actual Benefit	In dual therapy in combination with insulin: not applicable In triple therapy, in combination with insulin and metformin, TRAJENTA does not provide any improvement in actual benefit (IAB V, non-existent) in the management of type 2 diabetic patients in whom this combination alone, with diet and physical exercise, does not provide adequate glycaemic control. The Committee points out, as it had already said in its Opinion of 20 June 2012, that the level of evidence of data in patients aged over 70 years or with severe renal impairment is not sufficiently good to allow evaluation of the additional benefit contributed by TRAJENTA in these populations.
Therapeutic use	TRAJENTA has no place in therapeutic use in the management of type 2 diabetic patients in dual therapy in combination with insulin. In triple therapy, TRAJENTA is a treatment option that can be added to the combination of insulin + metformin.
Recommendations	The Transparency Committee would like the follow-up study[1] requested in June 2012 to be extended to the patients concerned by this extension of indication.

[1] This study, requested by the Committee in its Opinion of 20 June 2012, must have the objective "to describe in a real treatment situation:

- the characteristics of the patients treated (including age, BMI, the HbA1c value at the start of treatment, renal, hepatic and cardiac function);
- the conditions under which this proprietary medicinal product is used (indication, dosage and dose adjustments, concomitant treatments, methods used to monitor blood glucose, etc.) ;
- the maintenance level of treatment;
- the frequency of discontinuations and the reasons for them;
- the change in the HbA1c value and weight, as well as hypoglycaemia and long-term safety (2 years)."

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Starting date (centralised procedure): 24 August 2011 Date of the extension of indication: 24 October 2012
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, excluding insulins
	A10BH	Dipeptidyl peptidase-4 (DPP-4) inhibitors
	A10BH05	Linagliptin

02 BACKGROUND

This is an application for the inclusion of two new indications in the treatment of type 2 diabetes for the proprietary medicinal product TRAJENTA, i.e. in dual therapy in combination with insulin and in triple therapy in combination with insulin and metformin.

Linagliptin obtained a European Marketing Authorisation on 24 August 2011 in the treatment of type 2 diabetes, in monotherapy, in dual therapy in combination with metformin and in triple therapy in combination with metformin and a sulphonylurea.
In its Opinion of 20 June 2012, the Committee ruled as follows:
- insufficient AB in monotherapy,
- a substantial AB in dual therapy and triple therapy. The IAB in these indications was as follows: *"The level of evidence of data in patients aged over 70 years with severe renal impairment is not sufficiently good to allow assessment of the additional benefit contributed by TRAJENTA in these populations. There are no data with a sufficient level of evidence versus active comparators. Its efficacy seems to be of the same order of magnitude as that of the other substances in its class and its safety profile is similar.*
The Transparency Committee therefore considers that TRAJENTA does not provide any improvement in actual benefit (IAB V) in the management of type 2 diabetes patients in dual oral therapy, combined with metformin and as triple oral therapy, combined with metformin and a sulphonylurea."

The proprietary medicinal product TRAJENTA is not currently included on the list of medicines refundable by National Health Insurance or on the list of medicines approved for hospital use.

It was pointed out that linagliptin it is eliminated mainly in a non-metabolised form via the bile and the intestines. Thus, no dose adjustment is required in patients with renal impairment, whatever the severity stage of the renal impairment.

03 THERAPEUTIC INDICATIONS

"TRAJENTA is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults:

As monotherapy
- in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to intolerance, or contraindicated due to renal impairment.*

In combination:
- with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.*
- in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.*
- with insulin, with or without metformin, when this regimen alone, with diet and exercise, does not provide adequate glycaemic control."

** Indications already assessed by the TC (see opinion of 20 June 2012)*

04 DOSAGE IN THE NEW INDICATION

"The dose of linagliptin is 5 mg once daily. […]
When linagliptin is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia (see section 4.4).

Special populations
Patients with renal impairment
For patients with renal impairment, no dose adjustment for TRAJENTA is required.

Patients with hepatic impairment
Pharmacokinetic studies suggest that no dose adjustment is required for patients with hepatic impairment but clinical experience in such patients is lacking.

Elderly patients
No dose adjustment is necessary based on age.
However, clinical experience in patients over 80 years of age is limited and caution should be exercised when treating this population.

Paediatric population
The safety and efficacy of linagliptin in children and adolescents has not yet been established. No data are available.

Method of administration
TRAJENTA can be taken with or without a meal at any time of the day. If a dose is missed, it should be taken as soon as the patients remembers. A double dose should not be taken on the same day."

05 THERAPEUTIC NEED

Type 2 diabetes is a chronic and progressive disease, associated with substantial morbidity and mortality due to the micro- and macrovascular complications that it causes. Chronic hyperglycaemia is the main pathogenic element in microvascular complications (retinopathy,

nephropathy, neuropathy) and one of the components of macrovascular risk (coronary artery disease, arteritis of the lower limbs).

The aim of treatment is glycaemic control, i.e. control of HbA1c and control of associated risk factors.

The choice of drug therapy and the aims of treatment should be tailored to the individual patient (age, duration of diabetes, particular situations, hypoglycaemic risk, etc.).
Patients with type 2 diabetes are initially treated using lifestyle and dietary measures (actively combating a sedentary lifestyle, plus meal planning) which are essential actions at all stages in the management of this disease.
Antidiabetic drugs are introduced when diet and lifestyle changes are no longer sufficient to control blood glucose levels.

The latest updates of the international guidelines present approaches derived from the results of large trials (VADT, ACCORD, ADVANCE and 10-year follow-up results from UKPDS) and the introduction of incretin mimetics (GLP-1 analogues and DPP-4 inhibitors or gliptins).
The NICE guidelines[2] position DPP-4 inhibitors in dual or triple therapy and recommend their maintenance only if a significant reduction in the HbA1c level (-0.5%) is achieved in 6 months.
The latest ADA/EASD guidelines[3] propose adjustment of the target HbA1c (7% to reduce the microvascular risk). These guidelines, updated in 2012[4] and those of SIGN (Scottish Intercollegiate Guidelines Network),[5] now propose blood glucose targets centred on the patient. They position DPP-4 inhibitors in dual therapy as an alternative to sulphonylureas in patients in whom hypoglycaemia or weight gain may be a problem. They recognise switching from one dual therapy to another dual therapy as an alternative to direct escalation.

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 go on achieving their blood glucose 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.[3]
In the event of contraindications to or intolerance of metformin, sulphonylureas 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.
Sitagliptin was regarded by the Committee as a treatment option that can be added to the insulin/metformin combination (see Opinion of 18 July 2012) or insulin alone in patients with moderate to severe renal impairment (see Opinion of 19 September 2012). It is emphasized that this therapeutic situation (triple therapy in combination with insulin and metformin) was not mentioned in the good practice guidelines updated by HAS in January 2013 on glycaemic control in type 2 diabetes.

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

[3] 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.*

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

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

06 CLINICALLY RELEVANT COMPARATORS

The clinically relevant comparators of the medicinal product assessed are medicinal products available at the same stage of therapeutic use and intended for the same population, on the date of the assessment.

In this case, these are medicines indicated in type 2 diabetes:
- in dual therapy in combination with insulin
- in triple therapy in combination with insulin and metformin.

06.1 Medicinal products

INN	Same TC*	Name (Company)	Date of opinion	AB	IAB	Reimburse-ment
Biguanide						
Metformin and its generics	No	GLUCOPHAGE (Merck Santé)	21 July 2010 (RI)	Substantial		Yes
Insulin secretagogues						
Sulphonylureas and their generics	No			Substantial		Yes
Alpha-glucosidase inhibitors (acarbose, miglitol)	No	GLUCOR (Bayer Santé) DIASTABOL (Sanofi Aventis)	5 September 2012 (RI)	Substantial		Yes
Injectable incretin mimetic or GLP-1 analogues						
Exenatide	No	BYETTA (Lilly)	Not assessed by the TC[6]			
Gliptins						
Sitagliptin and its fixed combinations with metformin	Yes	JANUVIA 100 mg/ XELEVIA 100 mg (MSD, Pierre Fabre)	18 July 2012 (extension of indication)	In dual therapy in combination with insulin: insufficient actual benefit In triple therapy in combination with insulin and metformin: substantial actual benefit	Not applicable IAB V	No Yes
Sitagliptin	Yes	JANUVIA / XELEVIA 25 mg and 50 mg[7] (MSD, Pierre Fabre)	19 September 2012 (inclusion)	In dual therapy in combination with insulin: moderate AB In triple therapy in combination with insulin and metformin: insufficient AB	IAB V Not applicable	In progress
Vildagliptin and its fixed combinations with metformin	Yes	GALVUS / JALRA (Novartis)	Not assessed by the TC[8]			
Saxagliptin and its fixed combination with metformin	Yes	ONGLYZA (Bristol-Myers Squibb)	Still being assessed by the TC			

*TC = therapeutic category

[6] On 16 February 2012 BYETTA (exenatide) received a favourable opinion from the CHMP in the following extension of indication: "BYETTA is also indicated in combination with basal insulin with or without metformin and/or pioglitazone in adults without adequate glycaemic control with these medicines."
[7] JANUVIA 25 mg and JANUVIA 50 mg are two new dosages intended for dosage adjustment in patients with type 2 diabetes and moderate to severe renal impairment or end-stage renal disease.
[8] 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 a stable dose of insulin with diet and exercise do not provide adequate glycaemic control."

06.2 Other health technologies

Not applicable

Conclusion

Metformin and sulphonylureas are clinically relevant comparators in dual therapy in combination with insulin.

In triple therapy, in combination with insulin and metformin, the comparators with Marketing Authorisation are a GLP-1 analogue and the gliptins. They cannot be regarded as relevant.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSEMENT	
	YES - Date of start of reimbursement / NO If no, why not	Population(s) That of the Marketing Authorisation or restricted
USA	Yes 11/05/2011	All indications are eligible for reimbursement
Canada	Yes 01/02/2012	3rd line treatment when the patient is inadequately controlled or when insulin is not a treatment option
UK	Yes 19/09/2011 Assessment in progress for complete indications	In England and in Scotland, 2nd line treatment in combination with metformin
Germany	Assessment in progress	
Spain	Yes 16/01/2012	All indications are eligible for reimbursement
Italy	Assessment in progress	
Netherlands	Yes 01/04/2012	Monotherapy, dual therapy and triple therapy when insulin is not an option
Norway	Yes 01/05/2012	98% reimbursement in monotherapy (contraindication to or intolerance of metformin), in combination with metformin and metformin + sulphonylurea. Reimbursement if the maximum dose of metformin and/or sulphonylurea administered and if insulin is not an option.
Australia	Yes 01/04/2012	Listed on the PBS (pharmaceutical benefit scheme) in combination with metformin or a sulphonylurea

08 ANALYSIS OF AVAILABLE DATA

The company submitted the following data in support of its application:

- a pivotal randomised double-blind study (study 1218.36), assessing linagliptin versus placebo in combination with insulin therapy, with or without oral antidiabetics, in patients inadequately controlled by insulin therapy in a stable dose;
- an additional analysis of the data for patients treated with insulin during the study performed in patients with renal impairment (study 1218.43);
- a grouped analysis of the results of the pivotal study and study 1218.63 performed in patients over 70 years of age.

Studies 1218.43 and 1218.63, since they have already been evaluated by the Committee for the application for inclusion of TRAJENTA (see Opinion of 20 June 2012), cannot be used by the Committee in assessing the benefit of the combination of linagliptin and insulin, with or without metformin, for the reasons set out below.
Study 1218.43, performed randomised and double blind, evaluated the efficacy and safety of linagliptin versus placebo in 133 patients with severe renal impairment[9] who were not on dialysis, for 12 weeks of treatment and 40 weeks of follow-up.
The combined treatments[10] were:

- insulin in 56.1% of patients on linagliptin (37/66) and 69.4% of patients on placebo (43/62). This subgroup of patients could have been used to evaluate dual therapy with insulin + linagliptin,
- an oral antidiabetic drug (OAD) alone in 21.1% of patients on linagliptin (14/66) and 17.7% of patients on placebo (11/62), mainly a sulphonylurea which was contraindicated in patients with severe renal impairment,
- insulin + OAD (sulphonylurea) in 22.7% of patients on linagliptin (15/66) and 12.9% of patients on placebo (8/62). This triple therapy is not that of the Marketing Authorisation for TRAJENTA (which is in combination with insulin and metformin). This triple therapy could not have been evaluated in this study, since metformin is contraindicated in patients with renal impairment.

Analyses not provided for in the study protocol in these 3 subgroups of small numbers of patients have no demonstrative value. They therefore cannot be used by the Committee.

Study 1218.63, performed randomised 2:1 and double-blind, compared, in 241 type 2 diabetic patients over 70 years of age and already stable on treatment with metformin and/or sulphonylurea and/or insulin, the efficacy and safety of linagliptin (n = 162) with those of placebo (n = 79) for 24 weeks. Most patients were treated with 2 or 3 antidiabetic drugs (60.1%), 84.9% of patients were treated with metformin, 55.1% with a sulphonylurea and 21% with insulin.[10]
Treatment subgroup analyses were provided for in the protocol but were exploratory (no adjustment for the significance level, overestimate of effect not excluded). In addition, in the subgroup treated with insulin, there is only the overall result for the administration of insulin alone or in combination, but no data on the combination of insulin with linagliptin or the combination insulin + linagliptin + metformin.
This study is therefore not admissible. The grouped analysis of its results with those of the pivotal study therefore cannot be used.

It should be noted that the methods of studies 1218.43 and 1218.63 had given rise to reservations (evaluation in situations which are not those of the Marketing Authorisation, short duration of the study, adjustment of the doses of the combined treatments, small number of patients, many

[9] This study included 19 patients with moderate RI and 114 with severe RI (68 in the linagliptin 5 mg group, 65 in the placebo group)
[10] Dose adjustments for these treatments were permitted from the twelfth week onwards.

discontinuations of treatment, etc.) when TRAJENTA was examined for its inclusion (see Opinion of 20 June 2012).

Safety data were also supplied:

- data from the first two PSURs,
- an update of the specific meta-analysis of cardiovascular events that occurred during the clinical development of linagliptin,
- a grouped analysis of the safety data from the aforementioned 3 clinical studies (not used for the reasons given above).

08.1 Efficacy

8.1.1 Study 1218.36: in combination with insulin with or without oral antidiabetics

Aim and methods: Phase III, randomised, double-blind study the aim of which was to compare the efficacy and safety of the combination of insulin + linagliptin with those of the combination of insulin + placebo with or without oral antidiabetics (OADs), metformin and/or pioglitazone[11] after 52 weeks of treatment.

The protocol provided for stratified randomisation according to the treatment combined with OAD, renal function and the Hb1Ac level on inclusion.

Inclusion criteria:
Type 2 diabetic patients, inadequately controlled (HbA1c level ≥ 7% and ≤ 10%) by insulin therapy with basal insulin (insulin glargine, insulin detemir, NPH insulin) alone or combined with metformin and/or pioglitazone.

Non-inclusion criteria: treatment with rosiglitazone, sulphonylureas, GLP-1 analogues, gliptins in the last 3 months, hepatic impairment, history of cardiovascular event (myocardial infarction, CVA, transient ischaemic accident) in the last 6 months, contraindications to metformin or pioglitazone.[12]

Dosing regimen:
1263 patients were randomised to receive:
- either the combination basal insulin + linagliptin 5 mg/day ± metformin ± pioglitazone (n=633)
- or the combination basal insulin + placebo ± metformin ± pioglitazone (n=630).

During the first 24 weeks of treatment, the doses of basal insulin and/or OAD prescribed on randomisation had to remain stable. The protocol nevertheless provided for the possibility of increasing the doses of insulin by up to 10% of the dose used at the time of randomisation during this phase. From the 24th week to the end of the study, this adjustment was permitted.

Primary efficacy endpoint:
Mean change in the HbA1c level after 24 weeks of treatment compared with the baseline value (interim analysis provided for in the protocol).

The protocol provided for the inclusion of 600 patients in each of the treatment groups in order to demonstrate a difference of 0.35% ± 1.2% in respect of the change in the HbA1c level with a power of 93% and an overall significance level of 0.05.

[11] The study took place from August 2009 to September 2011. At that time, pioglitazone was still recommended and used in France. Pioglitazone-based proprietary medicinal products were deleted on 15 November 2011 following the Committee's Opinion of 20 July 2011: inadequate AB in all indications, namely monotherapy, dual therapy, triple therapy and in combination with insulin – opinion in favour of deletion from the lists of proprietary medicinal products reimbursed by National Health Insurance and approved for hospital use.

[12] Main contraindications to metformin: renal impairment, to pioglitazone: heart failure, hepatic impairment, bladder cancer.

Analyses for this endpoint specified in the protocol were performed in subgroups of patients (based on their blood-glucose-lowering treatment on inclusion, initial HbA1c level, BMI and the duration of diabetes). As no adjustment method was applied to take account of multiple comparisons, there might have been an overestimation of the effect. Consequently, no conclusions can be drawn on the basis of these exploratory analyses, and they are not presented.

Main secondary endpoints:
- Mean change in the HbA1c level at 52 weeks
- mean change in fasting blood glucose (FBG) after 52 weeks of treatment
- percentage of patients with an HbA1c level < 7% after 24 and 52 weeks of treatment
- safety (incidence of hypoglycaemic events, weight change, incidence of specific events: hypersensitivity – hepatic/renal events – pancreatitis).

Other criterion:
Use of a rescue therapy[13]

Results:

The results are from the analysis of all randomised patients who received at least one dose of treatment and for whom the HbA1c level was measured on inclusion and at least once during the first 24 weeks of treatment[14] (618/633 patients in the linagliptin group, 617/630 patients in the placebo group).

On inclusion, the characteristics of the patients in the two treatment groups were similar. They were:
- mean age 60 years (33% of patients were 65 or over),
- in most cases obese (mean BMI about 31.0 kg/m^2).

The duration of diabetes was more than 5 years in most patients.
The mean HbA1c level on inclusion was 8.3 ± 0.9%. About 40% of patients had an HbA1c of between 8 and 9%, 34.2% an HbA1c level of less than 8% and 22.8% an HbA1c level of ≥ 9%.
All patients were treated with basal insulin, 16% of them with insulin alone, 75.6% with a combination of insulin + metformin, 1% with a combination of insulin + pioglitazone and 7.4% with a combination of insulin + metformin + pioglitazone.

The mean dose of basal insulin was 40.9 U/day in all the randomised patients. The most commonly administered insulin was insulin glargine (47.7% of patients).
The mean dose of metformin received was 1995 mg in the linagliptin group and 1963 mg in the placebo group with large differences in dose.
Pioglitazone was prescribed in 8.5% of patients in a mean dose of 32 mg.

134/1261 patients included in the study had renal impairment:
- 127 patients (10.1%) had moderate renal impairment (GFR between 30 and 60 ml/min),
- 7 patients (0.6%) had severe renal impairment (GFR < 30 ml/min).

[13] A rescue treatment was considered to be any increase of more than 10% in the dosages of basal insulin, any change in OAD dosage or any introduction of a new oral antidiabetic therapy during the 52 weeks of treatment.
[14] FAS population as defined by the protocol

Table 1: Main characteristics of the patients included

	Placebo group N=630	Linagliptin group N=631	Total N=1261
Mean age (standard deviation, SD)	**60.4 (10.0)**	**59.7 (9.9)**	**60.0 (10.0)**
Age N (%)			
< 65 years	408 (64.8)	431 (68.3)	839 (66.5)
65-74 years	181 (28.7)	165 (26.1)	346 (27.4)
≥ 75 years	41 (6.5)	35 (5.5)	76 (6.0)
Mean BMI on inclusion (kg/m^2) (SD)	**31.16 (4.94)**	**30.78 (5.43)**	**30.97 (5.19)**
BMI on inclusion N (%)			
< 25 kg/m^2	63 (10.0)	91 (14.4)	154 (12.2)
> 25 and < 30 kg/m^2	206 (32.7)	207 (32.8)	413 (32.8)
≥ 30 kg/m^2	361 (57.3)	333 (52.8)	694 (55.0)
Mean basal HbA1c values (SD)*	**8.29 (0.85)**	**8.31 (0.85)**	**8.30 (0.85)**
Basal values HbA1c (category) [N (%)]			
< 7.0%	24 (3.9)	23 (3.7)	47 (3.8)
7.0% to < 8.0%	204 (33.1)	218 (35.3)	422 (34.2)
8.0% to < 9.0%	249 (40.4)	235 (38.0)	484 (39.2)
≥ 9.0%	140 (22.7)	142 (23.0)	282 (22.8)
Treatments on inclusion N (%)			
Patients on insulin without OAD	102 (16.5)	96 (15.5)	198 (16.0)
Metformin alone	464 (75.2)	470 (76.1)	934 (75.6)
Pioglitazone alone	6 (1.0)	6 (1.0)	12 (1.0)
Metformin + pioglitazone	45 (7.3)	46 (7.4)	91 (7.4)
Time since diagnosis of diabetes N (%)*			
Up to one year	12 (1.9)	14 (2.3)	26 (2.1)
1 to 5 years	66 (10.7)	86 (13.9)	152 (12.3)
> 5 years	539 (87.4)	518 (83.8)	1057 (85.6)
Basal GFR N (%)			
≥ 90 ml/min	275 (43.7)	277 (43.9)	552 (43.8)
60 to < 90 ml/min	283 (44.9)	292 (46.3)	575 (45.6)
30 to < 60 ml/min	68 (10.8)	59 (9.4)	127 (10.1)
< 30 ml/min	4 (0.6)	3 (0.5)	7 (0.6)

* values from the FAS (full analysis set) population: placebo group N = 617, linagliptin group N = 618

Primary efficacy endpoint:

Table 2: Change in HbA1c level at 24 weeks:

Treatment groups	N	Mean initial HbA1c level (standard deviation)	Adjusted mean change in HbA1c level (SD)	Mean difference versus comparator, 95% CI, p
Insulin + placebo ± metformin ± pioglitazone	617	8.29 (0.03)	0.07 (0.08)	
Insulin + linagliptin ± metformin ± pioglitazone	618	8.31 (0.03)	-0.58 (0.08)	**-0.65 [-0.74; -0.55] p<0.0001**

After 24 weeks of treatment, the reduction in the HbA1c level was greater in patients on insulin + linagliptin ± OAD than in those on insulin + placebo ± OAD (difference between linagliptin and placebo: -0.65%, 95%CI [-0.74; -0.55]; p<0.0001). We do not have any results for the insulin + linagliptin and insulin + metformin + linagliptin subgroups with a sufficient level of evidence.
It should be noted that sitagliptin was most effective up to the 18th week of treatment. HbA1c levels increase after that point.

Secondary endpoints:

- Mean change in the HbA1c level at 52 weeks

After 52 weeks of treatment, the HbA1c level increased by 0.05 ± 0.08% in the placebo group and fell by 0.48 ± 0.08% in the linagliptin group, a difference versus placebo of -0.53% 95% CI [-0.64; -0.43], p<0.0001. It should be noted that adjustments to the insulin doses were permitted during this period.[15]

- Mean change in fasting blood glucose (FBG) after 52 weeks of treatment

After 52 weeks of treatment, the fasting blood glucose level changed from 151 mg/dl (initial value) to 136 mg/dl in the placebo group and from 147 mg/dl to 136 mg/dl in the linagliptin group; there was no statistical analysis of the difference between groups.

- Percentage of patients with an HbA1c level < 7% after 24 and 52 weeks of treatment

The treatment objective of insulin therapy was achieved:
- by 19.5% of the patients analysed in the linagliptin group (116/618) and 8.1% of patients in the placebo group (48/617) after 24 weeks of treatment,
- by 15.8% of the patients analysed in the linagliptin group (94/618) and 6.6% of patients in the placebo group (39/617) after 52 weeks of treatment.

Other criterion: Use of a rescue therapy
The percentage of patients who needed rescue treatment at least once was greater in the placebo group (311/617 patients, 50.4%) than in the linagliptin group (236/618 patients, 38.2%).

08.2 Adverse effects

8.2.1 Data from study 1218.36

There was at least one adverse event in 81.4% of the patients on placebo (513/630) and 78.4% of the patients on linagliptin (495/631).

The main adverse events observed were:
- disorders of metabolism and nutrition for 49% of patients on placebo and 46% of patients in the linagliptin group (mainly hypoglycaemia in about 30% of patients),
- infections (mainly nasopharyngitis, urinary infections and infections of the upper airways) in 39.4% of patients on placebo, 37.9% of patients on linagliptin,
- musculoskeletal conditions in about 20% of patients (141 on placebo, 128 on linagliptin),
- gastrointestinal disorders, mainly diarrhoea and nausea, in about 20% of patients (126 on placebo, 140 on linagliptin),
- nervous system conditions, mainly headaches, for 17.8% of patients on placebo, 16.8% of patients on linagliptin,
- cardiovascular events (myocardial infarction, CVA, hospitalisation due to unstable angina, death) in 11 patients in the placebo group and 18 patients in the linagliptin group.

These events were considered to be linked to the treatment in 22.2% of the patients in the placebo group (140 patients) and 18.7% of the patients in the linagliptin group (118 patients). The

[15] There was a greater reduction in the dose of insulin (>10%) in the linagliptin group and a greater increase in the dose (>10%) in the placebo group.

commonest event attributable to the treatment was hypoglycaemia in 15.1% (95 patients) in the placebo group and 13.2% (83 patients) in the linagliptin group.
Severe adverse events were observed in 52 patients in each of the groups.

In the patients who did not have renal impairment, the incidence of adverse events was the same in the 2 treatment groups (78.2% of patients in the placebo group, 77.3% of the patients in the linagliptin group). For patients with moderate or mild renal impairment, the incidence of adverse events was greater in the placebo group (82.7% of patients) than in the linagliptin group (78.8%).

After 52 weeks of treatment:

- the number of patients with asymptomatic or symptomatic hypoglycaemia was 207/630 (32.9%) in the placebo group and 198/631 (31.4%) in the linagliptin group, 17.8% (112/630) of patients on placebo and 16.2% (102/631) on linagliptin had at least 3 hypoglycaemic episodes;
- 37.5% of patients on placebo and 37.9% of patients treated with linagliptin had at least one asymptomatic episode of hypoglycaemia, 22.9% (144/630) of patients in the placebo group, 24.9% (157/631) in the linagliptin group had at least 3 episodes.

A total of 52 patients reported at least 1 prespecified adverse event: 31/631 patients in the linagliptin group and 21/630 patients in the placebo group.
The following were observed:
- renal events[16] in 5 patients on placebo, 2 on linagliptin,[17]
- hepatic events[18] in 11 patients in the placebo group, 18 in the linagliptin group,
- hypersensitivity reactions (urticaria) in 4 patients on placebo, 7 on linagliptin,
- skin lesions in 1 patient in the linagliptin group,
- pancreatitis in 1 patient on placebo and 3 on linagliptin.[19]

No difference was observed in the change in weight between the placebo and linagliptin groups at 24 and 52 weeks of treatment.

The number of patients who discontinued treatment on account of adverse events was 28 in the placebo group and 21 in the linagliptin group.

8.2.2 SPC data

“In post-marketing experience of linagliptin, cases of acute pancreatitis have been reported spontaneously. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, intense abdominal pain. Resolution of pancreatitis has been observed after discontinuation of linagliptin. If pancreatitis is suspected, TRAJENTA should be discontinued.

Based on post-marketing experience for linagliptin, by analysing reports from spontaneous sources, angioedema (frequency rare) and urticaria (frequency rare) have been identified as additional adverse effects. (Frequency estimates are based on the pooled analysis of placebo controlled trials).

As regards cardiovascular risk, in an updated prospective, prespecified meta-analysis of independently confirmed cardiovascular events from 15 phase III clinical studies (ranging from 18 weeks to 24 months’ duration) involving 8622 patients with type 2 diabetes, linagliptin treatment was not associated with an increase in cardiovascular risk. The primary endpoint, the composite of the occurrence or time to first occurrence of CV death, non-fatal myocardial infarction, non-fatal stroke or hospitalisation for unstable angina, was non-significantly lower for linagliptin versus

[16] 4 acute renal impairment and 3 renal impairment
[17] In the linagliptin group, these 2 patients had renal impairment on randomisation. In the placebo group, out of the 5 patients, 4 patients had renal impairment on randomisation, the other patient had normal renal function.
[18] including an increase in GGT, ALT, AST, hepatic enzymes – steatosis – hepatic fibrosis – oesophageal varices.
[19] These 3 patients had a history of hepatobiliary disease concomitantly with their diabetes.

combined active and placebo comparators (RR = 0.83 95% CI [0.57;1.21]). In total there were 56 events on linagliptin and 55 on comparators. To date there is no evidence of an increased CV risk but the number of events in the clinical studies precludes any firm conclusions. However, cardiovascular events were similar between linagliptin and placebo (1.06% with linagliptin vs 1.21% with placebo)."

8.2.3 Data from the first 2 PSURs (periods from 2 May 2011 to 2 November 2011 and from 3 November 2011 to 2 May 2012)

Analysis of these PSURs showed 29 cases of pancreatitis and 3 cases of hypersensitivity.

08.3 Summary & discussion

Linagliptin in combination with insulin therapy, with or without oral antidiabetics OAD (metformin and/or pioglitazone) in type 2 diabetes, was evaluated in a randomised double-blind study versus placebo in 1261 inadequately controlled patients, mean age 60 years, most of them obese, who were treated for 52 weeks. The protocol made provision for an interim analysis of the mean change in HbA1c level after 24 weeks of treatment (primary efficacy endpoint).

On inclusion, the mean HbA1c level was 8.3 ± 0.9%.
All patients were treated with basal insulin: 16% of patients were treated with insulin alone, 75.6% received the combination insulin + metformin, 1% the combination insulin + pioglitazone (off-label) and 7.4% the combination insulin + metformin + pioglitazone (quadruple therapy not recommended).
It should be noted that linagliptin has no indication in combination with pioglitazone, use of which has been obsolete in France since 2011.

After 24 weeks of treatment, the reduction in HbA1c level was greater in patients on insulin + linagliptin ± OAD than in those on insulin + placebo ± OAD (difference between linagliptin and placebo: -0.65%, 95% CI [-0.74; -0.55]; p<0.0001).
The effect of linagliptin on HbA1c levels was greatest up to the 18th week of treatment then it declined.
We do not have any results with a sufficient level of evidence for patients treated with the combination insulin + metformin + linagliptin, the only relevant combination.

The mean change in HbA1c level at 52 weeks was subjected to exploratory analysis. No conclusion can be drawn from this result.
The level of patients who achieved an HbA1c level of < 7% on insulin therapy was:
- 19.5% of patients in the linagliptin group (116/618) and 8.1% of patients in the placebo group (48/617) after 24 weeks of treatment,
- 15.8% of patients in the linagliptin group (94/618) and 6.6% of patients in the placebo group (39/617) after 52 weeks of treatment.

The main adverse events observed were hypoglycaemia and infections (mainly nasopharyngitis, urinary infections and infections of the upper airways).
Adverse events specific to gliptins were reported in a total of 52 patients: renal events (2 patients on linagliptin versus 5 on placebo); hepatic events (18 versus 11 patients); urticaria (7 versus 4 patients); pancreatitis (3 versus 1 patient); skin lesions (1 patient on linagliptin).
The change in weight at 24 and 52 weeks of treatment did not differ between placebo and linagliptin.

The European Risk Management Plan, in addition to standard pharmacovigilance, includes in particular monitoring of the following risks: hypoglycaemia (particularly in combination with a sulphonylurea), pancreatitis and hypersensitivity reactions, angioedema and urticaria. The potential risks identified are skin disorders, infections and the risk of a decline in kidney function.

Hypersensitivity reactions and skin disorders will be specifically described in the PSURs.
The cardiovascular safety data are from relatively small populations.

Most of the patients (75%) were on triple therapy with insulin/metformin/linagliptin; data for the evaluation of insulin/linagliptin dual therapy are limited.
A comparison group with an optimised insulin therapy regimen would have been useful in determining the benefit of adding linagliptin.

The efficacy data available for diabetic patients with renal impairment or for elderly patients are limited.

In addition, in triple therapy in combination with insulin and metformin, it is impossible to evaluate patients with severe renal impairment, since metformin is contraindicated in these patients.
It is therefore difficult to evaluate the efficacy of linagliptin in patients with renal impairment.

Overall, the effect of linagliptin is similar to the degree of effect observed within the category. This effect, evaluated mainly in triple therapy in combination with insulin and metformin, is modest in terms of the reduction in the HbA1c level compared with existing alternatives[20] but of the same order of magnitude as that observed with the other gliptins.[21, 22, 23, 24] The authors of a meta-analysis of 29 trials evaluating the efficacy and safety of incretin mimetics concluded that their efficacy was modest (reduction in HbA1c level compared with placebo of -0.74%, 95% CI [-0.85; -0.62] for the gliptins, non-inferiority compared with active comparators).

No study has shown that linagliptin is superior in its Marketing Authorisation indications by comparison with a reference treatment.[25]
There are no morbidity and mortality data but 2 studies are in progress.

08.4 Programme of studies

Among the studies currently under way:

- the CAROLINA study aims to demonstrate the cardiovascular safety of linagliptin (comparison of linagliptin with a sulphonylurea, glimepiride, in terms of the occurrence of cardiovascular events). [26]

[20] Mean changes in HbA1c levels were:
- -1 to -1.5% with metformin
- -1 to -1.5% with sulphonylureas
- -0.8% with glinides
- -0.5 to 1% with alpha-glucosidase inhibitors.

[21] Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. Renee E. Amori et al. JAMA 2007; 298 (2) : 194-206
[22] Richter B. and al. Dipeptidyl peptidase-4 inhibitors for type 2 diabetes mellitus. The Cochrane Database of Systematic Reviews 2008, Issue 2
[23] Don Dicker and al. DPP-4 inhibitors. Impact on glycemic control and cardiovascular risk factors. Diabetes Care, Vol 34, Supplement 2, May 2011
[24] After 24 weeks of treatment, the reduction in the HbA1c level (primary efficacy endpoint) was greater in patients taking insulin + sitagliptin ± metformin than in those on insulin + placebo ± metformin (difference between sitagliptin and placebo: -0.56%, 95% CI [-0.70; -0.42]; p<0.001). This reduction is of the same order of magnitude in the strata of patients who did or did not receive metformin (see TC Opinion JANUVIA / JANUMET / XELEVIA / VELMETIA of 18 July 2012).
[25] T. Karagiannis and al. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. BMJ 2012 Mar 12;344:e1369. doi: 10.1136/bmj.e1369.
[26] This study started in October 2010. In February 2012, 3578 patients had been randomised out of the planned 6000. The end of recruitment was scheduled for the end of November 2012. The results are expected in 2018.

- the CARMELINA study, performed at the request of the FDA, aims to compare linagliptin with a placebo in terms of the occurrence of cardiovascular and/or renal events in diabetic patients at high cardiovascular risk who already have a renal disorder. [27]

- study 1218.64 aims to demonstrate the efficacy and safety of linagliptin *versus* placebo in patients with moderate to severe renal impairment (report expected in 2013).

09 THERAPEUTIC USE

Gliptins (including linagliptin) have no place in therapeutic use in the management of type 2 diabetic patients in dual therapy in combination with insulin.

Linagliptin is a treatment option that can be added to the combination of insulin + metformin in patients who do not achieve or maintain blood glucose targets with a combination of insulin and metformin.

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

010.1.1. In dual therapy in combination with insulin:

Type 2 diabetes is a chronic disease with potentially serious complications, particularly cardiovascular ones.
TRAJENTA would be 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 the sulphonylureas,
- the absence of any study comparing the combination insulin + linagliptin versus insulin + metformin or versus insulin + sulphonylurea which could have quantified the benefit and contribution of this dual therapy,
- the small number of patients treated with insulin alone (16%) in the study comparing linagliptin with a placebo, in combination with insulin,
- the long-term risks particularly in relation to cardiac, hepatic, pancreatic and cutaneous adverse events, which are poorly defined,
the efficacy/adverse effect ratio for TRAJENTA in dual therapy in addition to insulin cannot be quantified.

In view of the available data, this proprietary medicinal product cannot be recommended in dual therapy in combination with insulin. In fact, when initiating insulin treatment, metformin is the reference treatment to combine with it. In a systematic review[28] of 23 studies which included a total of 2117 patients and assessed metformin combined with insulin versus insulin alone, the

[27] Its protocol is being finalised, 8300 participating patients are planned. The results are expected in 2018.
[28] 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.

combination of insulin + metformin was associated, by comparison with insulin alone, with a larger reduction in HbA1c level (difference between groups of -0.60% 95% CI [-0.89; -0.31] p<0.001) and with weight gain (+ 1 kg). According to the guidelines,[3, 5] when insulin therapy is started to maintain or improve glycaemic control, the following dual therapies, insulin + metformin or insulin + sulphonylurea, 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 sub-population of patients with an indication for TRAJENTA as dual therapy is considered to be moderate.

The improvement of the therapeutic management of type 2 diabetics is a public health need which is an established priority.[29]

In the light of the results of the clinical study performed versus placebo of glycaemic control alone, the proprietary medicinal product TRAJENTA is not expected to have an impact on morbidity and mortality or on the quality of life of the patients treated by comparison with the dual therapies currently available.

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 including its effect on glycaemic control.

In the current state of knowledge, TRAJENTA cannot be expected to offer any response to the identified public health need.

Consequently, it is not expected that the proprietary medicinal product TRAJENTA will benefit public health.

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

010.1.2. In triple therapy in combination with insulin and metformin

Type 2 diabetes is a chronic disease with potentially serious complications, particularly cardiovascular ones.
TRAJENTA would be used in the context of treatment for hyperglycaemia.

The efficacy/adverse effects ratio for this medicinal product is high. However, the long-term risks, particularly in relation to cardiac, hepatic, pancreatic and cutaneous adverse events, are poorly defined.

It is a treatment for use in triple therapy after the failure of the combination insulin/metformin.

Alternative medicinal products exist.

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 sub-population of patients with an indication for TRAJENTA in triple therapy is considered to be moderate.

The improvement of the therapeutic management of type 2 diabetic patients is a public health need which is an established priority.[29]

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

In the light of the results of the clinical study of glycaemic control alone performed versus placebo, the proprietary medicinal product TRAJENTA is not expected to have an impact on morbidity and mortality or on the quality of life of the patients treated by comparison with the triple therapies currently available.
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 including its effect on glycaemic control.
In the current state of knowledge, TRAJENTA cannot be expected to offer any response to the identified public health need.
Consequently, it is not expected that the proprietary medicinal product TRAJENTA will benefit public health.

Consequently, the Committee considers that the actual benefit of TRAJENTA is substantial in triple therapy, in combination with insulin and metformin when this combination alone, with diet and exercise, does not provide adequate glycaemic control.

- **In dual therapy in combination with insulin:**

The Committee does not recommend inclusion of the proprietary medicinal product TRAJENTA on the list of medicines refundable by National Health Insurance or on the list of medicines approved for hospital use.

- **In the indication triple therapy in combination with insulin and metformin:**

The Committee recommends inclusion of the proprietary medicinal product TRAJENTA on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the aforementioned indication and at the dosage in the Marketing Authorisation.

Proposed reimbursement rate: 65%

010.2 Improvement in actual benefit (IAB)

- In dual therapy in combination with insulin: not applicable

- In triple therapy in combination with insulin and metformin:

In triple therapy, in combination with insulin and metformin, TRAJENTA does not provide any improvement in actual benefit (IAB V, non-existent) in the management of type 2 diabetic patients in whom this combination alone, with diet and physical exercise, does not provide adequate glycaemic control.

The Committee points out, as it had already said in its Opinion of 20 June 2012, that the level of evidence of data in patients aged over 70 years with severe renal impairment is not sufficiently good to allow assessment of the additional benefit contributed by TRAJENTA in these populations.

010.3 Target population

The target population of TRAJENTA in triple therapy consists of type 2 diabetic patients inadequately controlled (HbA1c > 7%) by the combination of insulin and metformin.

As a reminder, the prevalence of pharmacologically treated diabetes in France was estimated by National Health Insurance to be 4.4 % in 2009,[30] i.e. 2.9 million people. The annual growth rate is estimated to be 4.7% (rate calculated using data from only the general scheme).
Given the prevalence in 2009 and its progression and bearing in mind that the rate of progression is stable in the absence of any more recent data, the prevalence of treated diabetes would be almost 3.02 million people in 2012.
The 2007-2010 data from the ENTRED study also provide further details.[31, 32, 33]
91.9% of diabetic patients are said to be type 2 diabetics, which is about 2.78 million people.

[30] Ricci P, Blotière PO, Weill A, Simon D, Tuppin P, Ricordeau P, Allemand H. Diabète traité : quelles évolutions entre 2000 et 2009 en France ? *BEH 2010; 42-43: 425-31*

[31] The French 'Representative national sample of the Diabetic Population' (ENTRED) 2007-2010 Diaporama : Caractéristiques des personnes diabétiques, risque vasculaire, complications et prise en charge médicale (updated on 12 March 2010).

[32] Fagot-Campagna A, Fosse S, Roudier C, Romon I, Penfornis A, Lecomte P, Bourdel-Marchasson I, Chantry M, Deligne J, Fournier C, Poutignat N, Weill A, Paumier A, Eschwège E, for the ENTRED Scientific Committee. Caractéristiques, risque vasculaire et complications chez les personnes diabétiques en France métropolitaine : d'importantes évolutions entre Entred 2001 et Entred 2007. BEH. *2009; 42-43: 450-455*

[33] Fagot-Campagna A, Romon I et al (Institut de veille sanitaire) Prévalence et incidence du diabète, et mortalité liée au diabète en France *http://www.invs.sante.fr/publications/2010/plaquette_diabete/plaquette_diabete.pdf*

➢ Population of the indication in combination with insulin + metformin:

Populations considered	Numbers considered	Comments	Sources
Patients treated with insulin in 2007 (23% of T2D patients in 2007)	358,000		TC Opinion on LANTUS (2009)
- of which insulin alone (39.0%) **- of which insulin + OAD (61.0%)**	139,620 218,380	14.1% of T2D patients are treated with insulin, of which 5.5% with insulin alone	ECODIA 2 study, March 2007
Sub-population on insulin+OAD - 51.5% with HbA1c > 7%	218,380 112,465		ECODIA 2 study, March 2007
Total target population in this indication	**112,465 patients**		

In total, the target population for TRAJENTA in the extension of indication in triple therapy, in combination with insulin and metformin, is estimated to be at most 113,000 patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

Appropriate for the prescription conditions.

◗ Request for data

The Transparency Committee would like the follow-up study[1] requested in June 2012 to be extended to patients affected by this extension of indication.