HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

20 June 2012

TRAJENTA 5 mg, film-coated tablets
B/30 (CIP code: 217 743-5)

Applicant: BOEHRINGER INGELHEIM FRANCE

Linagliptin
ATC code: A10BH05 (DPP-4 inhibitor or gliptin)

List I

Date of Marketing Authorisation (centralised procedure): 24 August 2011

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Linagliptin

1.2. 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.

as combination therapy:
- 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."

1.3. Dosage

“The dose of linagliptin is 5 mg once daily. When linagliptin is added to metformin, the dose of metformin should be maintained and linagliptin administered concomitantly.
When linagliptin is used in combination with a sulphonylurea, a lower dose of the sulphonylurea 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 elderly patients > 75 years of age is limited.

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.”

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2012)

A: alimentary tract and metabolism
A10: drugs used in diabetes
A10B: blood glucose lowering drugs, excl. insulins
A10BH: dipeptidyl peptidase-4 (DPP-4) inhibitors,
A10BH05: linagliptin

2.2. Medicines in the same therapeutic category

Comparator medicines: dipeptidyl peptidase-4 inhibitors (DPP-4), gliptins

The table below gives the different indications for DPP-4 inhibitors together with the Committee's conclusions.

Marketing Authorisation Indications	JANUVIA / XELEVIA (sitagliptin)	GALVUS / JALRA (vildagliptin)	ONGLYZA (saxagliptin)
Second-line monotherapy: in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindication or intolerance.	**x** *still being evaluated by the Committee*	-	-
Dual therapy: in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.	**x**	**x**	**x**
Dual therapy:[1] in combination with a sulphonylurea and diet in patients inadequately controlled by sulphonylurea alone and for whom metformin is inappropriate.	**x**	**x**	**x**
Triple therapy: in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these two medicinal products do not provide adequate glycaemic control.	**x**	-	-
In combination with insulin	**x** *still being evaluated by the Committee*	-	-
Transparency Committee (TC) conclusions / date of opinion	Actual benefit substantial , **improvement in actual benefit IV** in the management of type 2 diabetes in patients treated with metformin as monotherapy, when diet, exercise and metformin do not provide adequate glycaemic control (TC Opinion of 6 June 2007 for JANUVIA and 19 December 2007 for XELEVIA) Actual benefit substantial, **improvement in actual benefit V** in the management of type 2 diabetes as triple therapy (TC Opinion of 24 June 2009)	Actual benefit substantial, **improvement in actual benefit V** in the management of patients with type 2 diabetes (TC Opinion of 10 December 2008 for GALVUS, of 7 September 2011 for JALRA).	Actual benefit substantial, **improvement in actual benefit V** in the management of type 2 diabetes patients as oral dual therapy, combined with metformin. (TC Opinion of 2 December 2009).

[1] This indication has not been accepted by the registration authorities who considered that the difference observed at 18 weeks (-0.47% 95% CI [-0.7; -0.24]) in the placebo-controlled study was not clinically relevant.

2.3. Medicines with a similar therapeutic aim

- As second-line monotherapy in type 2 diabetes patients inadequately controlled by diet or exercise and in whom metformin is contraindicated or not tolerated:
  - sulphonylureas,
  - alpha-glucosidase inhibitors (acarbose),
  - repaglinide.

- As dual therapy combined with metformin: in patients with type 2 diabetes who are not achieving adequate glycaemic control despite maximum tolerated doses of oral monotherapy with metformin:
- sulphonylureas,
- alpha-glucosidase inhibitors: (acarbose),
- repaglinide,
- GLP-1 analogues administered by injection: exenatide (BYETTA) and liraglutide (VICTOZA)

- As oral triple therapy combined with metformin and sulphonylureas in type 2 diabetes patients inadequately controlled by dual therapy with metformin and sulphonylurea at the maximum tolerated doses:
- insulins,
- GLP-1 analogues administered by injection: exenatide (BYETTA) and liraglutide (VICTOZA)

3 ANALYSIS OF AVAILABLE DATA

The clinical development of linagliptin (TRAJENTA) is based on:
- three double-blind, randomised, phase III placebo-controlled studies, performed as monotherapy in inadequately controlled patients and in whom metformin is contraindicated or poorly tolerated (study 1218.50); as dual therapy combined with metformin in patients inadequately controlled by metformin alone (study 1218.17); as triple therapy combined with a sulphonylurea and metformin (study 1218.18). Most of these studies included an open follow-up period of 78 weeks.
- a study performed as monotherapy in a general population of diabetic patients (study 1218.16), not described as it was outside the Marketing Authorisation indication
- a non-inferiority study versus active comparator, glimepiride combined with metformin (study 1218.20)
- a double-blind, randomised, phase III placebo-controlled study performed in patients with severe renal failure (study 1218.43)
- a double-blind, randomised, phase III placebo-controlled study performed in patients aged over 70 years (study 1218.63)

Among the trials currently taking place, the CAROLINA study will be aiming to demonstrate the cardiovascular safety of linagliptin (comparison of linagliptin with a sulphonylurea, glimepiride, in terms of onset of cardiovascular events).

3.1. Efficacy results

3.1.1. Results of studies performed in the Marketing Authorisation indications

Table 1: Summary of the methodology and studies

Studies		Methods				Efficacy results	General safety		
	Aims: to evaluate efficacy and safety in type 2 diabetes patients	Study design	Duration (weeks)	Patient characteristics (mean values)	Treatment regimens:	Primary efficacy endpoint: change in HBA1c (%) value Main secondary endpoint: % of patients achieving an HbA1c value <6.5% or <7%	Change in weight	Patients who had had hypoglycaemia	Overall safety, % of patients with an adverse event
1218.50	**<u>Monotherapy</u> combined with diet in patients with metformin intolerance or contraindication** **N=227**	Double-blind, randomised placebo-controlled study	18 + 34 weeks of open follow-up	56.5 years BMI = 29.46 kg/m2 HbA1c value = 8.09% 75% patients diagnosed within the previous 5 years	Randomisation 2 :1 Linagliptin 5 mg group (n = 151) Placebo group (n = 76)	HbA1c (linagliptin – placebo) = -0.57 ± 0.14% 95% CI [-0.86; -0.29] p<0.0001 at 52 weeks: HbA1c =-0.78% % patients at clinical endpoint (HbA1c < 6.5%): 6.8% in the placebo group, 9.5% in the linagliptin group	weight (linagliptin – placebo) = 0.81 ± 0.53 kg 95% CI [−0.25; 1.86] P NS	Linagliptin group: 2 patients Placebo group: 0 patients	Linagliptin group: 40.4%, Placebo group: 48.7%
1218.17	**<u>Dual therapy</u> Evaluation of linagliptin combined with metformin in patients inadequately controlled by metformin alone at a dose ≥ 1500 mg/day** **N = 701**		24 + 78 weeks of open follow-up	56.5 years BMI = 29.9 kg/m2 HbA1c value = 8.08% 54.9% of patients diagnosed more than 5 years previously	Randomisation 3:1 Linagliptin 5 mg + metformin group (n = 523) Placebo + metformin group (n = 177)	HbA1c (linagliptin – placebo) = -0.64 ± 0.07% 95% CI [-0.78; -0.50] p <0.0001 % patients at clinical endpoint (HbA1c < 7%): 11.4% in the placebo group, 28.3% in the linagliptin group	weight (linagliptin – placebo) = 0.216 ± 0.349 kg 95% CI [-0.469; 0.901] P NS	Linagliptin group: 3 patients Placebo group: 5 patients	Linagliptin group: 55.4%, Placebo group: 52.8%

1218.18	**<u>Triple therapy</u>** **Evaluation of linagliptin combined with metformin + sulphonylurea dual therapy in patients inadequately controlled by this dual therapy** **N = 1058**		24	58.1 years BMI = 28.3 kg/m2 HbA1c value = 8.14% 73.3% patients diagnosed more than 5 years previously	Randomisation 3:1 Linagliptin 5 mg + metformin+SU group (n = 792) Placebo + metformin + SU group (n = 263)	HbA1c (linagliptin – placebo) = -0.62 ± 0.06% 95% CI [-0.73; -0.50] p < 0.0001 % patients at clinical endpoint (HbA1c < 7%): 9.2% in the placebo group, 31.2% in the linagliptin group	weight (linagliptin – placebo) = 0.33 ± 0.19 kg 95% CI [-0.04; 0.69] P NS	Linagliptin group: 188 patients (23.7%) Placebo group: 42 patients (16.0%)	Linagliptin group: 66.3%, Placebo group: 59.7%
1218.20	**<u>Dual therapy</u>** **Evaluation of linagliptin combined with metformin versus metformin + sulphonylurea dual therapy in patients inadequately controlled by metformin alone.** **Total N = 1552**	Randomised, double-blind study versus active treatment (metformin + glimepiride) Non-inferiority study Non-inferiority threshold: 0.35% (per-protocol analysis)	104 (52+ 52)	59.8 years BMI = 30.26 kg/m2 HbA1c value = 7.69% 52.9% patients diagnosed more than 5 years ago	Randomisation 1:1 Linagliptin 5 mg/day + metformin group (n = 775) Glimepiride 2.74 mg/day + metformin group (n =777)	<u>At 52 weeks</u> HbA1c (linagliptin – glimepiride) = 0.22 ± 0.04% 97.5% CI [0.13, 0.31] <u>At 104 weeks</u> HbA1c (linagliptin – glimepiride) = 0.20 ± 0.05% 97.5% CI [0.09; 0.299] Upper CI limit < 0.35 % patients at clinical endpoint (HbA1c<7%): 34.8% in the glimepiride group, 30.4% in the linagliptin group	<u>At 52 weeks</u> weight (linagliptin – glimepiride = -2.49 ± 0.18 kg 95% CI [-2.89, -2.08] p<0.0001 <u>At 104 weeks</u>: weight (linagliptin – glimepiride = -2.68 ± 0.22kg 95% CI [-3.17, -2.19] p<0.0001	Five times more hypoglycaemia in the glimepiride vs linagliptin group 52 weeks Linagliptin 42 patients (5.4%) Glimepiride 248 patients (31.8%) 104 weeks Linagliptin 58 patients (7.5%) Glimepiride 280 patients (36.1%)	Linagliptin group: 85.4%, Glimepiride group: 91.1%

✓ *Monotherapy study*

In this study; patient characteristics at inclusion were similar in each treatment group.
Mean patient age was approximately 56 years and most patients (79%) were under 65 years of age. Mean BMI was 29.46 kg/m2 (at the threshold of obesity).
75% of patients had been diagnosed with type 2 diabetes within the previous five years, and 22.7% of them had been diagnosed within the previous year.
HbA1c value was 8.09% in both treatment groups (placebo and linagliptin).
More than half of the patients (54.1%) were treatment-naive (for at least 10 weeks at the time of preselection). Around 45% of patients were treated with an oral anti-diabetic (34.5% with a sulphonylurea,[2] 10.9% with metformin[3]).
Most of the patients were intolerant of metformin (gastrointestinal events occurred for 93% of the patients included), i.e. 7% had a contraindication to metformin.
The difference observed versus placebo in terms of change in HbA1c value (-0.57% 95% CI [-0.86; -0.29] p<0.0001) was in favour of linagliptin after 18 weeks of treatment.
This difference was maintained at 52 weeks, after 34 weeks of open follow-up.
9.5% of patients in the linagliptin group (14/151) and 6.8% of patients in the placebo group (5/76) reached the clinical endpoint at this stage of patient management (HbA1c value < 6.5%).

✓ *Dual therapy studies*

In the placebo-controlled study 1218.17, mean patient age was 56.5 years and the patients were overweight (mean BMI 29.9 ± 4.9 kg/m2). HbA1c values were similar in both treatment groups: 8.0% in the placebo group, 8.1% in the linagliptin group. 68.6% of the patients enrolled had previously taken a single anti-diabetic drug (metformin) and 31.4% had taken two anti-diabetic drugs (sulphonylurea + metformin in the vast majority of cases: 26.9% of patients).
Most of the patients were diagnosed more than 5 years ago (54.9%). Only 11% of patients had a recent diagnosis (≤ 1 year). The mean dose of metformin was 1875.5 mg in the metformin + linagliptin group, and 1952.7 mg in the metformin + placebo group.
After 24 weeks of treatment there was a statistically significant reduction in HbA1c value of 0.64% in favour of linagliptin compared with placebo.
The clinical target of dual therapy, an HbA1c value < 7%, was achieved by 28.3% of patients included in the linagliptin group (145/513) and 11.4% of patients in the placebo group (20/175).

In study 1218.20 with a total population of 1552 patients inadequately controlled by metformin alone, mean patient age was 59.8 years, patients were obese (BMI of 30.26 kg/m2, 50.5% of patients enrolled had BMI > 30) and most patients had been diagnosed more than 5 years ago (52.9% of patients). Only 7.1% of patients had been diagnosed recently (≤ 1 year).
HbA1c value at inclusion was 7.69% in both treatment groups.
70.4% of the patients included in the study had previously taken a single anti-diabetic drug (metformin) and 29.5% were taking two anti-diabetic drugs (in 26.1% of patients in the glimepiride group and 25.7% of patients in the linagliptin group, this was the combination metformin + sulphonylurea).
After 52 and 104 weeks of treatment, as the upper 97.5% CI limits were higher than the predefined non-inferiority threshold (0.35%), the metformin + linagliptin combination was shown to be non-inferior to with the combination metformin + sulphonylurea (glimepiride).
However, around 50% of patients included had not received the maximum dose of glimepiride (4 mg/day). Treatment discontinuations because of lack of efficacy involved 5.8% of patients in the linagliptin + metformin group and 1.9% of patients in the metformin + sulphonylurea group.

[2] i.e. 76 patients, 25 on placebo and 51 on linagliptin
[3] i.e. 24 patients, 10 on placebo and 14 on linagliptin

✓ *Triple therapy study*

This placebo-controlled study included a total of 1058 patients inadequately controlled by metformin + sulphonylurea dual therapy. Patients' characteristics were comparable between both treatment groups.

Mean patient age was 58 years, patients were overweight (mean BMI of 28.3 kg/m2), they had been diagnosed more than 5 years previously (73.3% of patients). Fewer than 3% of patients had been diagnosed recently (< 1 year).

HbA1c value was similar in both treatment groups: 8.14% in the metformin + sulphonylurea + placebo group and 8.15% in the metformin + sulphonylurea + linagliptin group.

Almost all of the patients were on dual therapy at inclusion (99.8%).

After 24 weeks of treatment there was a significant reduction in HbA1c of 0.62% compared with placebo (95% CI = [-0.73; -0.50%] with $p < 0.0001$).

The clinical endpoint, HbA1c value < 7%, was achieved by 31.2% of patients in the linagliptin group (243/792) and 9.2% of patients in the placebo group (24/263).

✓ *Data on open-label follow-up **of** these four studies*

Follow-up lasted for 78 weeks and involved 2121 patients.[4]

The secondary objective was to monitor maintenance of efficacy.

After 78 weeks of open follow-up, the mean reduction in HbA1c value was 0.57%.[5]

3.1.2. Results of the studies performed in specific populations

Table 2: Summary of design and studies

[4] 1880 patients completed the 78-week observation period.

[5] In patients pre-treated with linagliptin, efficacy was maintained (average change in HbA1c value = -0.1%). The mean reduction in HbA1c value in patients from the placebo groups was 0.67% compared with baseline.

Studies		Methods			Efficacy results	General safety		
	Aims: to evaluate the efficacy and safety in type 2 diabetes	Study design	Patient characteristics (mean values)	Treatment regimens:	Primary efficacy endpoint: Change in HBA1c (%)value at 12 weeks Primary secondary endpoint: % of patients achieving an HbA1c value < 7%	Change in weight	Patients who had h hypoglycaemia	Overall safety, % of patients with an adverse event
1218.43	**Study performed in patients with severe renal failure (GFR < 30 ml/min) who were not on dialysis** **N = 133**	Double-blind, randomised placebo-controlled study Duration: 12+40 follow-up versus placebo	64.4 years BMI = 32.02 kg/m2 HbA1c value at inclusion = 8.2% 96.1% patients diagnosed more than 5 years ago Around 80% of patients treated with insulin 19 patients with moderate renal failure 114 with severe renal failure	Randomisation 1:1 Linagliptin group 5 mg (n = 68) Placebo group (n = 65) **No dose adjustment of combined treatments allowed before 12 weeks; adjustment of oral anti-diabetic drugs or insulin allowed after 12 weeks**	<u>At 12 weeks</u> HbA1c (linagliptin – placebo) = -0.59 ± 0.15% 95% CI [-0.88; -0.29] p < 0.0001 <u>At 52 weeks</u> (secondary endpoint) HbA1c (linagliptin – placebo) = -0.72 ± 0.16% 95% CI [-1.03; -0.41] p < 0.0001 % patients at clinical endpoint (HbA1c rate < 7%): 9.7% of patients in the placebo group, 18.2% of patients in the linagliptin group	<u>At 52 weeks</u> weight (linagliptin + placebo) = 0.22 ± 1.28kg 95% CI [0.13, 0.31] P NS	During the first 12 weeks, higher frequency of hypoglycaemia in the linagliptin group (33 patients, 48.5%) than in the placebo group (17 patients, 26.1%) From weeks 12 to 52 : hypoglycaemia observed in 34 patients under linagliptin (50%) and 30 patients under placebo (46%). a) Difference between linagliptin and placebo particularly concerned asymptomatic hypoglycaemia. b) Intergroup difference potentially attributed to whether or not the investigator could adjust treatment.	Linagliptin group: 92.3%, Placebo group: 94.1%

1218.63	**Study performed in elderly diabetic patients (> 70 years old) already on stable treatment with metformin and/or sulphonylurea and/or insulin** **N = 241**	Double-blind, randomised placebo-controlled study Duration: 24 weeks	74.9 years BMI = 29.67 kg/m2 HbA1c value = 7.78% 87.4% patients diagnosed more than 5 years previously Most patients taking 2 or 3 anti-diabetic drugs 21% treated with insulin 55.1% treated with sulphonylurea Around 85% on metformin	Randomisation 2:1 Linagliptin 5 mg group (n = 162) Placebo group (n = 79) **No dose adjustment of combined treatments allowed before 12 weeks**	HbA1c (linagliptin + placebo) = -0.64± 0.08% 95% CI [-0.81; -0.48] p < 0.0001 % patients at clinical endpoint (HbA1c rate<7%): 11.5% of patients in the placebo group, 41.9% of patients in the linagliptin group (p<0.0001)	Mean change of –0.6 kg in the placebo group and -0.2 kg in the linagliptin group	Higher frequency of hypoglycaemia in the linagliptin group (39 patients, 24.1%) than in the placebo group (13 patients, 16.5%) Most cases of hypoglycaemia occurred in patients treated with sulphonylurea and/or insulin. a) Difference between linagliptin and placebo particularly concerned asymptomatic or mild hypoglycaemia. b) Possible post randomisation bias generated by a combination of no possibility of adjusting treatment and a greater proportion of hypoglycaemia-inducing combinations in the linagliptin group at the start of the study.	Linagliptin group: 75.9%, Placebo group: 75.9%

✓ *Study in patients with severe renal impairment*

Patients' demographic characteristics were comparable between both treatment groups. Mean age was 64.3 ± 10.3 years and most patients were at least 65 years of age (57%). Patients were obese and the vast majority were diagnosed more than 5 years previously (96.1%). Only 3.9% of patients had a more recent diagnosis (between 1 and 5 years). Patients with a history of myocardial infarction or stroke in the six months preceding the study were not enrolled.

Mean HbA1c value was 8.2%.

Concomitant treatments were:

- **insulin alone** in 56.1% of patients on linagliptin (37/66) and 69.4% of patients on placebo (43/62)
- **oral anti-diabetic drugs (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 failure
- **insulin + OAD (sulphonylurea)** in 22.7% of patients on linagliptin (15/66) and 12.9% of patients on placebo (8/62).

Five patients received metformin contraindicated in patients with renal failure (two in the placebo group and three in the linagliptin group).[6]

The study was to evaluate linagliptin in patients with severe renal failure (GFR < 30 mL/min). However, at randomisation, it was found that a certain number of patients with moderate renal failure (GFR between 30 and 60 ml/min) had been included. A total of 92.6% patients in the linagliptin group had severe renal failure compared with 78.5% of patients in the placebo group.

At 12 weeks of treatment, a statistically significant reduction of the HbA1c value was observed in favour of linagliptin compared with placebo (difference of -0.59 ± 0.15% 95% CI [-0.88; -0.29] p<0.0001).

At 52 weeks, the difference observed (secondary endpoint) could not be used as doses of concomitant treatments had been adjusted. It is therefore difficult to assess the size of the effect of linagliptin. The clinical target (HbA1c rate < 7%) was achieved by 18.2% (12/66) of patients from the linagliptin group and 9.7% of patients from the placebo group (6/62).

✓ *Study in the elderly:*

In this 24-week study in 241 patients, mean age was 74.9 years (44.4% of patients being over 75 years of age), and type 2 diabetes had been diagnosed more than 5 years previously in the majority of patients (87.4%) who were close to the threshold of obesity. HbA1c value was 7.78%.

Most patients were treated with two or three anti-diabetic drugs (60.1%), 84.9% of patients were treated with metformin, 55.1% with a sulphonylurea and 21% with insulin. Dose adjustment was allowed for these treatments from the twelfth week onwards. Very few patients benefited from such an adjustment in treatment (13.5% of patients from the placebo group, 5.6% of patients from the linagliptin group).

After 24 weeks of treatment a significant reduction of the HbA1c value of 0.64% was observed in favour of linagliptin compared with the placebo (95% CI = [-0.81; -0.48%] with p < 0.0001).

The clinical target (HbA1c < 7%) was achieved by 41.9% of patients under linagliptin and 11.5% of patients under placebo.

[6] At the severe renal failure stage, only insulin and glinides are indicated

3.2. Safety data

3.2.1. From placebo-controlled studies

In the three placebo-controlled studies (as monotherapy, dual therapy and triple therapy), 58.8% of patients treated with linagliptin (N = 1466) and 56.6% of patients from the placebo group (N = 516) had at least one adverse event.
The main adverse events were infections (predominantly nasopharyngitis) observed in 20.5% of patients under linagliptin and 24.6% of patients under placebo, metabolic and nutritional disorders (hyperglycaemia as monotherapy, dual therapy and triple therapy) in 21% of patients under linagliptin and 23% of patients under placebo.
No difference in terms of weight loss was observed.
Under triple therapy, hypoglycaemic events were more common in the linagliptin group as has already been observed with other anti-diabetic drugs combined with a sulphonylurea (23.7% of patients under linagliptin, 16% of patients under placebo). Most cases of hypoglycaemia were asymptomatic.
Treatment discontinuations because of adverse events involved 34 patients treated with linagliptin (including 23 in the triple therapy study mainly because of hypoglycaemia) and 8 from the placebo groups (including 5 from the triple therapy study).
Adverse events specific to gliptins (hypersensitivity, hepatic events, renal events) involved 13 patients under linagliptin and six patients under placebo.
The long-term data (up to 102 weeks) did not reveal any new reports of adverse events.

3.2.2. From the study versus active comparator

In the non-inferiority study versus glimepiride, 85.4% of patients in the linagliptin group and 91.1% of patients in the glimepiride group had at least one adverse event.
The most common adverse events were:
- infections (48.7% under linagliptin; 50.7% under glimepiride),
- musculo-skeletal and systemic disorders (33.1% in the linagliptin group; 31.5% in the glimepiride group)
- disorders of the central nervous system (19.2% in the linagliptin group; 23.4% in the glimepiride group)
- metabolic and nutritional disorders (18.6% under linagliptin; 44.1% under glimepiride)
- skin and subcutaneous disorders (15.3% of patients under linagliptin; 12.3% of patients under glimepiride).

Treatment discontinuations because of adverse events (predominantly hypoglycaemias) were more common in the glimepiride group (85 patients, 11.0%) than in the linagliptin group (60 patients, 7.7%).
The adverse events specific to gliptins (hypersensitivity, hepatic events, renal events) involved 16 patients from the glimepiride group and 14 patients from the linagliptin group.

Pre-defined cardiovascular events (CV mortality, myocardial infarction, strokes and hospitalisation for unstable angina pectoris) were observed in 12 patients (1.5%) under linagliptin and 26 patients (3.4%) under glimepiride. The relative risk of a cardiovascular event was 0.46 95% CI [0.23-0.91], p = 0.0213. The relative risk of a non-fatal stroke was 0.27, 95% CI [0.08, 0.97], p = 0.0315. There was no difference between treatments as far as other events were concerned. These data should be interpreted with care, as data for patients at high risk of a cardiovascular event are not available, as these patients were not included in the studies. Moreover, the number of cardiovascular events observed is low.

3.2.3. From the study in patients with severe renal failure

An adverse event was observed in 92.3% of patients from the placebo group, 94.1% of patients from the linagliptin group.
The most commonly occurring adverse events were: metabolic and nutritional disorders (70.8% of patients from the placebo group and 77.9% of patients from the linagliptin group) including hypoglycaemia in 63.2% on linagliptin and 49.2% on placebo, as well as infections (44.6% of patients from the placebo group and 48.5% of patients from the linagliptin group).
During the first 12 weeks when dose adjustments were not allowed, hypoglycaemia was reported in 26.1% of patients under placebo and 48.5% of patients under linagliptin. Subsequently, when dose adjustments were allowed, hypoglycaemia was reported in 46% of patients on placebo, 50% of patients on linagliptin.
The adverse events specific to gliptins (hypersensitivity, hepatic events, renal events) were observed in three patients from the placebo group and four patients from the linagliptin group.
Treatment discontinuations, predominantly because of adverse events, involved 17/65 patients (26.2%) from the placebo group and 19/68 patients from the linagliptin group (27.9%).

3.2.4. From the study in patients over 70 years of age

The percentage of patients having had an adverse event was similar in both treatment groups: 75.9% in both groups (60 patients from the placebo group and 123 patients from the linagliptin group).

The most common adverse events were the following:
- hypoglycaemia (16.5% in the placebo group, 24.1% in the linagliptin group),
- hyperglycaemia (10.1% in the placebo group, 5.6% in the linagliptin group),
- nasopharyngitis (8.9% of patients on placebo; 10.5% of patients on linagliptin),
- urinary infections (6.3% of patients on placebo; 4.3% of patients on linagliptin),
- upper respiratory tract infection (6.3% of patients from the placebo group, 3.7% of patients from the linagliptin group).

Most of the adverse events were mild to moderate in severity. Most cases of hypoglycaemia occurred in patients treated with a sulphonylurea and/or insulin.

Severe adverse events were observed in three patients in the placebo group and nine patients in the linagliptin group.
Adverse events specific to gliptins (hypersensitivity, hepatic events, renal events) involved four patients from the linagliptin group and none in the placebo group.
Treatment discontinuations because of adverse events involved one patient from the placebo group and eight patients from the linagliptin group.

3.2.5. From the first PSUR (period from 2 May 2011 to 2 November 2011)

Analysis of the PSUR showed eight cases of pancreatitis and three cases of hypersensitivity. The SPC should be modified to add the following adverse events: urticaria, angioedema, and peripheral oedema.

3.3. Conclusion

There was a statistically significant reduction in HbA1c value in favour of linagliptin compared with placebo :

- as monotherapy, in 227 patients inadequately controlled and in whom metformin was contraindicated or poorly tolerated. After 18 weeks of treatment, the difference between linagliptin and placebo was -0.57%, 95% CI [-0.86; -0.29] p < 0.0001
- as dual therapy in combination with metformin at non-optimum dosage (mean 1900 mg/day) in 701 patients inadequately controlled by metformin alone. After 24 weeks of treatment, the difference between metformin + linagliptin and metformin + placebo was -0.64%, 95% CI [-0.78; -0.50] p < 0.0001,
- as triple therapy in combination with a sulphonylurea and metformin in 1058 patients. After 24 weeks of treatment, the difference between metformin + sulphonylurea + linagliptin and metformin + sulphonylurea + placebo was -0.62%, 95% CI [-0.73; -0.50] p < 0.0001.

After 52 and 104 weeks of treatment, the non-inferiority of the metformin/linagliptin combination was established compared with the metformin/sulphonylurea (glimepiride) combination. However, the level of evidence for this non-inferiority was not optimal as non-maximum doses of glimepiride were used and treatment discontinuation due to lack of efficacy was more common in the metformin + linagliptin group than in the metformin + glimepiride group.[7]

In monotherapy, the clinical target (HbA1c rate < 6.5%) was achieved by 9.5% of patients in the linagliptin group (n = 151) and 6.8% of patients in the placebo group (n = 76).
In dual therapy, this target (HbA1c value < 7%) was achieved by 28.3% of patients from the linagliptin group (n = 513) and, 11.4% of patients from the placebo group (n = 175).
In triple therapy, the clinical target (HbA1c value < 7%) was achieved by 31.2% of patients from the linagliptin group (n = 792) and 9.2% of patients from the placebo group (n = 263).
The level of responders was low.

In a double-blind, randomised placebo-controlled study performed in 133 patients with renal failure (severe in 92.6% patients from the linagliptin group and 78.5% of patients from the placebo group), after 12 weeks of treatment, the reduction in HbA1c value was greater with linagliptin than with placebo (difference of -0.59 ± 0.15%; 95% CI [-0.88; -0.29] p < 0.0001). The clinical target (HbA1c value < 7%) was achieved by 18.2% of patients from the linagliptin group and 9.7% of patients from the placebo group. However, these results should be interpreted with caution for the following reasons:

- the majority of patients were treated with insulin and/or a sulphonylurea although linagliptin is not indicated in combination with these treatments.
- efficacy was measured at 12 weeks
- dose adjustment of concomitant treatments was allowed after 12 weeks of treatment
- the number of patients evaluated was low (n = 133)
- there were a large number of treatment discontinuations (around 27% in each treatment group)
- patients with renal impairment generally have a history of cardiovascular disease, and yet this type of patient was not included in the study.

In the study performed in 241 patients aged over 70 years, after 24 weeks of treatment, a significant reduction in the HbA1c value of 0.64% was observed in favour of linagliptin compared with placebo (95% CI [-0.81; -0.48%], p < 0.0001). The clinical target (HbA1c < 7%) was achieved by 41.9% of patients under linagliptin and 11.5% of patients under placebo. Nevertheless, the methodology of this study has given rise to some reservations (evaluation in situations which are not those of the Marketing Authorisation, short duration of the study, dose adjustment of concomitant treatments, low number of patients, etc.

[7] These same reservations were expressed during the evaluation of sitagliptin (see Opinion on JANUVIA from the Transparency Committee of 6 June 2007).

In terms of safety, the main adverse events observed were infections and hypoglycaemia.
The anti-diabetic treatments to be used in patients with impaired renal function and in elderly patients should not induce hypoglycaemia.[8] However, during the first 12 weeks when dose adjustments were not allowed, hypoglycaemia was more common with linagliptin than with placebo in the study in patients with severe renal impairment, a vulnerable population with an increased risk of cardiovascular disease (26.1% of patients under placebo and 48.5% of patients under linagliptin had hypoglycaemia). Subsequently, after the 12th week, when dose adjustments were allowed, 46% of patients on placebo and 50% of patients on linagliptin had hypoglycaemia. In the study in patients over 70 years of age, hypoglycaemia was observed in 16.5% of patients on placebo and 24.1% of patients on linagliptin, the majority of cases of hypoglycaemia involving patients treated with a sulphonylurea and/or insulin.

The European Risk Management Plan, in addition to standard pharmacovigilance, includes in particular monitoring of the following risks: hypoglycaemia, pancreatitis, cutaneous lesions (ulceration, erosion and cutaneous necrosis) and severe hypersensitivity reactions, opportunistic infection and deterioration of renal function.

Overall, the effect of linagliptin is similar to the degree of effect observed within the category. In dual or triple therapy, this effect is modest in terms of reduction in HbA1c value compared with existing alternatives[9] but of the same order of magnitude as that observed with the other gliptins.[10, 11, 12] 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 value compared with placebo of -0.74%, 95% CI [-0.85; -0.62] for the gliptins, non-inferiority compared with active comparators).
There is no direct comparison between linagliptin and saxagliptin in dual therapy or triple therapy even though the development times would have allowed this.
No study has shown that linagliptin is superior in its Marketing Authorisation indications to a reference treatment.[13]
There are no morbidity and mortality data but a study is underway.

[8] B. Detournay et al. Chronic kidney disease in type 2 diabetes patients in France: prevalence, influence of glycaemic control and implications for the pharmacological management of diabetes. Diabetes & Metabolism, March 2012, Vol 38, 102-112.
[9] Mean changes in HbA1c values 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.

[10] 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.
[11] Richter B. and al. Dipeptidyl peptidase-4 inhibitors for type 2 diabetes mellitus. The Cochrane Database of Systematic Reviews 2008, Issue 2.
[12] Don Dicker and al. DPP-4 inhibitors. Impact on glycemic control and cardiovascular risk factors. Diabetes Care, Vol 34, Supplement 2, May 2011.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

In monotherapy

Type 2 diabetes is a chronic disease with potentially serious complications, particularly cardiovascular complications.
The proprietary medicinal product TRAJENTA is a treatment for hyperglycaemia.

In the indication as monotherapy, the efficacy of TRAJENTA versus placebo is modest in terms of the reduction in HbA1c value (-0.57%) in view of the reduction observed with comparators such as metformin and sulphonylureas (roughly -1 to -1.5%), with a positive impact in terms of morbidity and mortality.[13] Moreover, the level of responders (HbA1c < 6.5%) to monotherapy with TRAJENTA is low (9.5%).
There are no data against an active comparator, particularly a sulphonylurea.
According to the wording in the Marketing Authorisation indication, TRAJENTA is intended for patients unable to tolerate metformin or who have a contraindication to metformin because of renal failure. However, in the study performed by the company, the number of patients included who had previously been treated with metformin was low (24/227, i.e. 10.9% of patients) and most of them were unable to tolerate metformin because of gastrointestinal events. In the case of contraindication to metformin, the available data are very limited and do not allow any evaluation of the benefit provided.
For these reasons, the efficacy/adverse effects ratio for TRAJENTA, as monotherapy, cannot be qualified.

In view of the available data, this proprietary medicinal product cannot be recommended as monotherapy. There are alternative drugs to this proprietary medicinal product in the management of diabetic patients with a contraindication to metformin, that is to say, predominantly sulphonylureas and insulin in patients with moderate renal impairment, and insulin in patients with severe renal impairment. In the event of failure of properly conducted monotherapy using drugs that have been proved to be effective, a change to dual therapy could be envisaged.

There are alternative drugs to this proprietary medicinal product.

Public health benefit:
The public health burden of type 2 diabetes is substantial because of its high prevalence, which is constantly increasing, and the concomitant microvascular and macrovascular complications. The public health burden in the sub-population of patients with an indication for TRAJENTA as monotherapy is also considered to be moderate.
Improvement in the treatment of type 2 diabetics is a public health need which comes within the framework of established priorities.[14] Access to effective and well-tolerated treatments for type 2 diabetes patients with renal impairment is a public health need.
In view of the results of the clinical study performed in this indication, no additional impact is expected on glycaemic control from the medicinal product TRAJENTA. Moreover, the available data do not make it possible to estimate the impact of TRAJENTA on morbidity and mortality and quality of life of type 2 diabetes patients compared with currently available monotherapies.
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.

[13] Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998, 352 , 854-65.
[14] 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 improvement plan for the quality of life of people with chronic diseases 2007-2011.

In the current state of knowledge, the proprietary medicinal product TRAJENTA is unable to offer any response to an identified public health need.

Consequently, no public health benefit is anticipated for the medicinal product TRAJENTA in this indication.

The transparency Committee therefore considers the actual benefit of the medicinal product TRAJENTA to be insufficient for it to be refundable by National Health Insurance, as monotherapy in patients inadequately controlled by diet and exercise alone and in whom metformin is not tolerated or contraindicated because of renal failure.

In dual therapy and triple therapy

Type 2 diabetes is a chronic disease with potentially serious complications, particularly cardiovascular complications.
The proprietary medicinal product TRAJENTA is a treatment for hyperglycaemia.
The efficacy/safety ratio is high. However, the long-term risks are poorly defined, particularly in relation to cardiac, hepatic, pancreatic and cutaneous adverse events.
TRAJENTA is a treatment to be used as dual therapy combined with metformin and as oral triple therapy combined with metformin and a sulphonylurea.
Alternative drugs exist to this proprietary medicinal product.

Public health benefit:
The public health burden of type 2 diabetes is substantial because of its high prevalence, which is constantly increasing, and the concomitant microvascular and macrovascular complications. The public health burden in the sub-population of patients with an indication for TRAJENTA as dual therapy or triple therapy is considered to be moderate.
Improvement in the treatment of type 2 diabetics is a public health need which comes within the framework of established priorities.[15] Access to effective treatments which are well tolerated in type 2 diabetes patients with renal impairment is a public health need.
In view of the results of the clinical studies performed in this indication, no additional impact is expected on glycaemic control from the proprietary medicinal product TRAJENTA. Moreover, the available data do not make it possible to estimate the impact of TRAJENTA on morbidity and mortality and quality of life of type 2 diabetic patients compared with currently available dual therapies and triple therapies.
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, the proprietary medicinal product TRAJENTA is unable to offer any response to an identified public health need.

Consequently, no public health benefit is anticipated for the proprietary medicinal product TRAJENTA.

The transparency Committee considers that the actual benefit of the proprietary medicinal product TRAJENTA is substantial in its indications as dual therapy combined with metformin and as triple therapy combined with a sulphonylurea and metformin.

[15] 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 improvement plan for the quality of life of persons with from chronic diseases 2007-2011

4.2. Improvement in actual benefit (IAB)

- In the indication as monotherapy: not applicable

- In the indications as dual therapy and triple therapy:

The level of evidence of data in patients aged over 70 years with severe renal impairment is not sufficiently good to allow evaluation 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 the other drugs 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 as dual oral therapy, combined with metformin and as triple oral therapy, combined with metformin and a sulphonylurea.

4.3. Therapeutic use

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.).
Type 2 diabetes patients should first be treated by diet and lifestyle measures which should be continued at all stages.
Oral anti-diabetic drugs are introduced when diet and lifestyle changes are no longer sufficient to control blood glucose levels.
Active measures against a sedentary lifestyle and dietary planning are essential interventions at all stages of diabetes management.
If HbA1c is > 6.5% despite the maximum dose of monotherapy, the following dual therapies should be prescribed:
- metformin + insulin secretagogue
- metformin + alpha-glucosidase inhibitor
- or insulin secretagogue + alpha-glucosidase inhibitor (in the case of high post-prandial hyperglycaemia, but this combination is less effective in reducing HbA1c value than the other combinations).

If HbA1c value is > 7%, triple therapy or insulin combined with metformin or another oral anti-diabetic drug apart from glitazones should be prescribed.
This treatment strategy is being revised by HAS. The role of GLP-1 analogues and DPP-4 inhibitors has yet to be established.

The latest updates of the international guidelines present approaches derived from the results of large trials (VADT, ACCORD, ADVANCE and results from the 10-year UKPDS follow-up survey) and the introduction of incretin mimetics.
The NICE guidelines[16] in particular make it possible to establish the role of existing DPP-4 inhibitors in dual and triple therapy. They also suggest that the treatments with new drugs can only be continued if a significant reduction in HbA1c value is achieved within 6 months, i.e. -0.5% for DPP-4 inhibitors, and -1% for exenatide (GLP-1 analogue).
The latest ADA/EASD guidelines[17] also propose adjustment of target HbA1c (7% to reduce the microvascular risk). These guidelines, updated in 2012[18] now propose an approach

[16] 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

[17] 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.*

[18] 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.

centred on the patient with individualised blood glucose targets. They also offer a treatment algorithm allowing practitioners to adjust treatment to the patient's situation.
The SIGN (Scottish Intercollegiate Guidelines Network) guidelines[19] recommend adjustment of target HbA1c values according to on the patient's profile,[20] they estimate the amount of effect of DPP-4 inhibitors[21] or gliptins, they describe the role of DPP-4 inhibitors in dual therapy as an alternative to sulphonylureas in patients in whom hypoglycaemia or weight gain may pose a problem, and they recognise as third-line treatment the change from dual therapy to another dual therapy as an alternative to direct escalation.

Therapeutic use of TRAJENTA
As the Committee does not have any direct comparison or a good level of evidence in comparison with the recommended dual therapies, it cannot determine the value of the combination metformin + linagliptin. TRAJENTA should be used predominantly in combination with metformin when metformin alone, combined with diet and regular exercise, does not provide adequate glycaemic control. There are also treatment alternatives.

As there are no direct comparisons with validated and available triple therapies, none can be recommended in preference to any of the others. TRAJENTA may be used in triple oral therapy, combined with a sulphonylurea and metformin when dual therapy with these medicines, combined with diet and regular exercise, does not provide adequate glycaemic control.

TRAJENTA is an additional means of treatment for the management of type 2 diabetes patients.
It has been reported that it is eliminated mainly in a non-metabolised form in the bile and gut, so no dose adjustment is required in patients with renal failure, whatever the stage of severity of the renal failure.

4.4. Target population

The target population for TRAJENTA is represented by type 2 diabetes patients treated with:
- metformin when diet, exercise and metformin do not provide adequate glycaemic control (HbA1c > 6.5%)
- metformin combined with a sulphonylurea when glycaemic control is inadequate despite a maximum tolerated dose of these two drugs, combined with dietary measures exercise (HbA1c > 7%).

The prevalence of diabetes treated with drug therapy in France has been estimated by the National Salaried Workers' Health Insurance Fund (CNAMTS) to be 4.4% in 2009,[22] that is 2.9 million people. In view of the 2009 prevalence and the rate of increase, the number of diabetic patients treated in 2010 would be almost 3.03 million people.
The 2007-2010 data from the ENTRED study also provide further details.[23,24, 25]
91.9% of diabetic patients would be type 2 diabetics, that is around 2.79 million people.

[19] Scottish Intercollegiate Guidelines Network SIGN; 2010, Management of diabetes. A national clinical guideline. http://www.sign.ac.uk/pdf/sign116.pdf
[20] A target value of 7.0% for HbA1c is a reasonable objective for reducing microvascular and macrovascular risk. A target value of 6.5% may be relevant at the time of diagnosis.
[21] Compared with placebo, sitagliptin, vildagliptin and saxagliptin have reduced HbA1c value by 0.7%, 0.6% and 0.6% respectively.
[22] Ricci P, Blotière PO, Weill A, Simon D, Tuppin P, Ricordeau P, Allemand H. Diabète traité : quelles évolutions entre 2000 et 2009 en France ? [Treated diabetes: developments in France between 2000 and 2009] *BEH 2010; 42-43: 425-31*
[23] The French 'Representative national sample of the Diabetic Population' (ENTRED) 2007-2010 Diaporama : Characteristics of diabetics, cardiovascular risk, complications and medical treatment] (updated on 12 March 2010).
http://www.invs.sante.fr/surveillance/diabete/entred_2007_2010/resultats_metropole_principaux.htm
[24] 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 [Characteristics, cardiovascular risk and, complications in diabetics in metropolitan France: important developments between Entred 2001 and Entred 2007]. BEH. *2009; 42-43: 450-455.*
[25] Fagot-Campagna A, Romon I et al (Institut de veille sanitaire) *Prévalence et incidence du diabète, et mortalité liée au diabète en France [Prevalence and rate of diabetes, and mortality due to diabetes in france]* [Prevalence and incidence of diabetes and diabetes-related mortality in France] http://www.invs.sante.fr/publications/2010/plaquette_diabete/plaquette_diabete.pdf

➢ Population for the indication for dual therapy combined with metformin in patients inadequately controlled by metformin alone

The number of patients treated with metformin alone can be estimated to be 557,000 on the basis of 83.2% of diabetic patients treated with oral anti-diabetic drugs alone without insulin, 24% of whom are treated with metformin alone.
The number of patients with HbA1c > 6.5% is estimated to be 45% according to the latest ENTRED data.
Therefore; the number of patients inadequately controlled by diet and by properly-conducted treatment with metformin would be 250,000 people.

➢ Population for the indication for triple therapy combined with metformin and a sulphonylurea in patients inadequately controlled by this dual therapy

The number of patients treated with dual therapy with metformin and a sulphonylurea as dual therapy is estimated to be 24.6% of patients treated with oral anti-diabetic drugs alone. This gives an estimated total of 571,000 patients.
The number of patients with HbA1c > 7% is estimated to be 50% according to the latest ENTRED data.
On this basis, the population of patients who fail properly conducted metformin and sulphonylurea dual therapy would therefore amount to 285,000 people.

The estimated total target population for TRAJENTA is a maximum of 535,000 patients.

4.5. Transparency Committee recommendations

➢ In the indication as monotherapy:

The transparency 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 and various public services.

➢ In the indications as dual therapy, combined with metformin and as triple therapy, combined with a sulphonylurea and metformin:

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indications and at the dosages given in the Marketing Authorisation.

Packaging: Appropriate for the prescription conditions.
Reimbursement rate: 65%

The transparency Committee would like a study to be carried out in a representative sample of French type 2 diabetes patients, treated with TRAJENTA. The aim of the study would be to describe the actual situation with regard to treatment:

- the characteristics of the patients treated (including age, BMI, the HbA1c value at 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.) ;
- level of maintenance of treatment;
- the frequency of discontinuations and the reasons for them;
- change in HbA1c value and weight, as well as hypoglycaemia and long-term safety (2 years).

Reasons should be given for choice of study duration, which should be decided on by a scientific committee, and the duration should be sufficiently long to respond to the questions raised by the Committee.
If planned or on-going studies, in particular within the remit of the European Risk Management Plan, do not answer all the questions raised by the Transparency Committee, a specific study must be conducted.