HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 September 2012

JANUVIA 25 mg, film-coated tablets
B/28 (CIP code: 379 246-7)
B/50 (CIP code: 570 708-1)

JANUVIA 50 mg, film-coated tablets
B/28 (CIP code: 379 249-6)
B/50 (CIP code: 570 710-6)

Applicant: MERCK SHARP & DOHME-CHIBRET

Sitagliptin
ATC code: A10BH01 (DPP-4 inhibitor or gliptin)

List I

Date of the initial Marketing Authorisation (centralised procedure): 21 March 2007
Amendment to the Marketing Authorisation of 22 December 2011 (deletion from the SPC of the precautions for use for sitagliptin in patients with renal impairment)

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance (B/28) and approved for hospital use (B/28 and B/50).

The applicant requests the inclusion of JANUVIA 25 mg on the list for use in patients with type 2 diabetes with severe renal impairment or end-stage renal disease treated by dialysis and of JANUVIA 50 mg for use in patients with type 2 diabetes with moderate renal impairment in the following indications:

- *as monotherapy,*
- *in combination with a sulfonylurea or insulin.*[1]

Medical, Economic and Public Health Assessment Division

[1] The company has excluded from its request the indications in combination with metformin. The reason for this is that metformin is contraindicated in patients with renal impairment, whatever the level of severity.

BACKGROUND: Development of sitagliptin in diabetic patients with renal impairment

During the initial Marketing Authorisation request for JANUVIA, a clinical study (study P028) was appended to the dossier examined by CHMP. This study evaluated the safety and efficacy of appropriate doses of sitagliptin (25 mg and 50 mg) in 65 patients with type 2 diabetes and moderate to severe renal impairment or end-stage renal disease treated by dialysis. In view of the small size of the patient population, the CHMP requested the implementation of supplementary studies in patients with diabetes and moderate, severe or end-stage renal disease within the framework of the Risk Management Plan (RMP).
The SPC, in the "precautions for use" section, states that: "*Clinical study experience with JANUVIA in patients with moderate or severe renal impairment is limited. Therefore, use of JANUVIA is not recommended in this population.***"**

Because the 25 and 50 mg dosages of JANUVIA are appropriate for patients with renal impairment and bearing in mind the restriction on use in patients with renal impairment, the inclusion of these dosages on the list of medicines refundable by National Health Insurance and the approval for hospital use was not requested in the initial request for inclusion of JANUVIA 100 mg on the list (dossier examined by the Transparency Committee [TC] in June 2007).

MSD has carried out the studies requested in the Marketing Authorisation: studies P063 (study to evaluate doses of 25 mg and 50 mg of sitagliptin in diabetic patients with moderate to severe renal impairment) and P073 (study to evaluate the 25 mg dose of sitagliptin in diabetic patients with end-stage renal disease treated by dialysis). These two studies permitted the removal, on 22 December 2011, of the restriction on the use of sitagliptin in diabetic patients with moderate to severe or end-stage renal disease.

JANUVIA, at dosages of 25 mg and 50 mg, has been granted Marketing Authorisation in the United States, in Australia, and in Japan. In Europe, these proprietary medicinal products are currently covered by the national health insurance systems in Germany and the United Kingdom.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Sitagliptin

1.2. Indications

“For adult patients with type 2 diabetes mellitus, JANUVIA is indicated to improve glycaemic control:

as monotherapy:
- in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindication or intolerance.

as dual oral therapy in combination with:
- metformin, when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- a sulfonylurea when diet and exercise plus maximal tolerated dose of a sulfonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
- a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e. a thiazolidinedione) when use of a PPARγ agonist is appropriate and when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control. (Obsolete indication not requiring evaluation by the TC, as glitazones are no longer available in France).

as triple oral therapy in combination with:
- a sulfonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.
- a PPARγ agonist and metformin when use of a PPARγ agonist is appropriate and when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. (Obsolete indication not requiring evaluation by the TC, as glitazones are no longer available in France).

JANUVIA is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dose of insulin do not provide adequate glycaemic control.”

To recap, the TC has concluded that, for JANUVIA 100 mg:

- as monotherapy: AB insufficient (see Opinion of 18 July 2012)
- as dual oral therapy in combination with:
• metformin: substantial AB, IAB IV (see Opinion of 6 June 2007)
• a sulfonylurea: low AB, IAB V (see Opinion of 24 June 2009)
- as triple oral therapy in combination with:
• a sulfonylurea and metformin: substantial AB, IAB V (see Opinion of 24 June 2009)
- in combination with insulin: AB insufficient (see opinion of 18 July 2012)
- in combination with insulin and metformin: substantial AB, IAB V (see Opinion of 18 July 2012).

1.3. Dosage

"The dose of JANUVIA is 100 mg once daily. When JANUVIA is used in combination with metformin, the dose of metformin should be maintained and JANUVIA administered concomitantly.

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

If a dose of JANUVIA is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day. JANUVIA may be taken with or without food.

Patients with renal impairment
When considering the use of sitagliptin in combination with another anti-diabetic product, its precautions for use in patients with renal impairment should be checked.
For patients with mild renal impairment (creatinine clearance [CrCl] ≥ 50 ml/min), no dose adjustment for JANUVIA is required.
For patients with moderate renal impairment (CrCl ≥ 30 to < 50 ml/min), the dose of JANUVIA is 50 mg once daily.
For patients with severe renal impairment (CrCl < 30 ml/min) or with end-stage renal disease requiring haemodialysis or peritoneal dialysis, the dose of JANUVIA is 25 mg once daily. JANUVIA may be administered without regard to the timing of dialysis.
Because there is a dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of JANUVIA and periodically thereafter.

Patients with hepatic impairment
No dose adjustment is necessary for patients with mild to moderate hepatic impairment. JANUVIA has not been studied in patients with severe hepatic impairment.

Elderly patients
No dose adjustment is necessary based on age. Limited safety data is available in patients ≥ 75 years of age and care should be exercised.

Paediatric population
JANUVIA is not recommended for use in children below 18 years of age due to a lack of data on its safety and efficacy."

1.4. Special warnings and precautions for use (see SPC)

"Hypoglycaemia when used in combination with other anti-hyperglycaemic agents
In clinical trials of JANUVIA as monotherapy and as part of combination therapy with agents that do not normally lead to hypoglycaemia (for example metformin), rates of hypoglycaemia reported with sitagliptin were similar to rates in patients taking placebo. When sitagliptin was added to a sulfonylurea or to insulin, the incidence of hypoglycaemia was increased over that of placebo. **Therefore, to reduce the risk of hypoglycaemia, a lower dose of sulfonylurea or insulin may be considered.**

Renal impairment
JANUVIA is renally excreted. To achieve plasma concentrations of JANUVIA similar to those in patients with normal renal function, lower dosages are recommended in patients with moderate to severe renal impairment as well as in patients with end-stage renal disease requiring haemodialysis or peritoneal dialysis (see sections 4.2 and 5.2).
When considering the use of sitagliptin in combination with another antidiabetic product, its precautions for use in patients with renal impairment should be checked.

Hypersensitivity reactions
There have been postmarketing reports of serious hypersensitivity reactions in patients treated with JANUVIA. **These reactions include anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with JANUVIA**, with some cases occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUVIA, assess for other potential causes of the event, and institute alternative treatment for diabetes.

Pancreatitis
In postmarketing experience, there have been spontaneously reported adverse reactions of acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of sitagliptin (with or without supportive treatment), but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, JANUVIA and other potentially suspect medicinal products should be discontinued."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2012)

A: Alimentary tract and metabolism
A10: Drugs used in diabetes
A10B: Blood glucose lowering drugs, excluding insulins
A10BH: Dipeptidyl peptidase-4 (DPP-4) inhibitors
A10BH01: Sitagliptin

2.2. Medicines in the same therapeutic category

JANUVIA 25 mg and JANUVIA 50 mg are two new dosages intended for dose adjustment in patients with type 2 diabetes and moderate to severe renal impairment or end-stage renal disease.
According to their SPCs, the indications for the use of other gliptins in cases of renal impairment (RI) are as follows:

- ONGLYZA 2.5 mg (saxagliptin), indicated in combination with metformin or a sulfonylurea, may be used in patients with type 2 diabetes who have moderate RI, with caution in patients with severe RI, and is not recommended in patients with end-stage renal disease requiring haemodialysis.
(Request for inclusion of this proprietary medicinal product examined by the TC on 7 September 2011; following the issuing of a draft Opinion on 21 September 2011, the request was withdrawn by the company. The TC classified the AB as insufficient)

- TRAJENTA (linagliptin), indicated in monotherapy, particularly where metformin is contraindicated because of renal impairment, in combination with metformin ± a sulfonylurea, may be used in patients with type 2 diabetes who have RI without dose adjustment.
(See TC Opinion of 20 June 2012 – AB insufficient in monotherapy, particularly where metformin is contraindicated because of RI, substantial AB and IAB V in dual therapy and triple therapy)

- GALVUS and JALRA (vildagliptin), indicated in monotherapy, in combination with metformin or a sulfonylurea, may be used in patients with moderate or severe RI and with caution in those with end-stage renal disease requiring dialysis.
Under evaluation by the TC, dossier submitted on 30 July 2012.

2.3. Medicines with a similar therapeutic aim

Table 1: Medicinal products with a similar therapeutic aim to JANUVIA 25 mg and 50 mg as a function of the degree of renal impairment (RI) in patients with type 2 diabetes

	Metformin	Sulfonylureas	Intestinal alphaglucosidase inhibitors	Glinides	GLP-1 analogues**	Insulin**
Moderate RI (Creatinine clearance 30 to 50 ml/min)	**CI**	**authorised**	**authorised**	**authorised**	**Exenatide: authorised Liraglutide: NR**	**authorised**
Severe RI (Creatinine clearance) < 30 ml/min	**CI**	**CI**	**CI†**	**authorised**	**NR**	**authorised**

CI: Contraindicated in the SPC.
NR: Not recommended in the "precautions for use" section of the SPC.
**: Administered by injection.
†: Contraindicated if the creatinine clearance is < 25 ml/min/1.73 m^2 .

3. ANALYSIS OF AVAILABLE DATA

The proprietary medicinal product JANUVIA already exists in the form of a different presentation with a dose of 100 mg. When its Marketing Authorisation was granted, it was accompanied by a European Risk Management Plan that included, among other things, the implementation of clinical studies in patients with type 2 diabetes and moderate, severe or end-stage renal disease, studies P063 and P073, which are the subject of this evaluation.

3.1. Efficacy results

3.1.1. Study P063

Aim and method: Randomised, double-blind, phase III study, to demonstrate, in monotherapy, the non-inferiority of sitagliptin to glipizide, in patients with type 2 diabetes inadequately controlled by diet and exercise alone and moderate to severe renal impairment,[2] after 54 weeks of treatment.

Inclusion in the study and randomisation were preceded by a washout phase during which the antidiabetic medication was discontinued and diet and physical activity were optimised (for 14 weeks), followed by 2 weeks of single-blind placebo treatment.[3]

The randomisation was stratified according to the severity of renal impairment (moderate/severe), cardiovascular disease history (with/without a history of cardiovascular, cerebrovascular, or peripheral vascular disease), and history of cardiac failure (with/without).

Inclusion criteria:
Patients with type 2 diabetes, at least 30 years of age, with moderate to severe renal impairment, inadequately controlled by diet and exercise alone (HbA1c level ≥ 7% and ≤ 9%) who have not received antidiabetic treatment for at least 3 months, or who are under treatment with antidiabetic monotherapy or low-dose dual therapy (dose ≤ 50% of the maximum recommended dose of each antidiabetic[4]) and with an HbA1c level ≥ 6.5% and ≤ 9%.

Principal exclusion criteria:
- Patients on dialysis
- Known cardiovascular disease (myocardial infarction or unstable angina) or angioplasty during the preceding 3 months
- Recent signs of cardiac failure or aggravation of cardiac failure in the 3 months preceding inclusion
- Severe peripheral vascular disease
- Recent episode or diagnosis of cerebrovascular accident, transient ischaemic attack, or neurological complaints, or recent changes of treatment for these complaints
- Treatment with a GLP-1 analogue or gliptin in the preceding 3 months.

Dosing regimen:
Four hundred and twenty-six (426) patients were randomised to receive:
- either sitagliptin at a dosage of 25 mg/day in case of severe renal impairment or 50 mg/day in case of moderate renal impairment (n = 211)

[2] Assessment of the glomerular filtration rate is based on the MDRD (*Modification of the Diet in Renal Disease*) formula and the stages of severity are as follows: moderate renal impairment is defined by a glomerular filtration rate of between ≥ 30 ml/min/1.73m^2 and < 50 ml/min/1.73m^2, severe renal impairment by a glomerular filtration rate < 30 ml/min/1.73m^2, and end-stage renal disease is defined by recourse to dialysis.
[3] Patients not receiving antidiabetic treatment were able to start the single-blind placebo treatment phase immediately.
[4] These drugs were discontinued during the pre-inclusion phase.

- or glipizide at an initial dose of 2.5 mg/day, which could be increased up to 20 mg/day (n = 212).

One centre did not follow good clinical practice, and its three patients were excluded from the analysis.
Patients with inadequate glycaemic control could be given insulin. To avoid an increase in the risk of hypoglycaemia, patients on glipizide discontinued their treatment once insulin treatment was initiated.

Primary efficacy endpoint:
Average change in HbA1c level after 54 weeks of treatment compared with the baseline value.

Sitagliptin could be considered non-inferior to glipizide if the upper limit of the 95% confidence interval of the difference between the two treatments (sitagliptin – glipizide) in respect of the criterion "change in the HbA1c level" was less than 0.4%.[5]
The protocol envisaged the inclusion of 162 patients in the *per protocol* analysis.

Secondary endpoints after 54 weeks of treatment:
- mean change in the fasting blood glucose level
- change in weight
- percentage of patients with an HbA1c level < 7%

The analyses of the subgroups specified in the protocol were carried out (age, body mass index, severity of renal impairment, HbA1c at inclusion, previous antidiabetic treatments and duration of diabetes). As no adjustment method was applied to take account of multiple comparisons, the possibility of an overestimation of the effect cannot be ruled out. Consequently, no conclusions can be drawn on the basis of these exploratory analyses, and they are therefore not presented.

Results:
At inclusion, the characteristics of the patients in the two treatment groups were similar.
On average, the patients were 64.6 years old (48.7% of the patients were aged 65 or over), and they were overweight (mean BMI 26.7 kg/m^2).
They had had diabetes for 10 years on average. Among the patients randomised, 78.2% of those in the sitagliptin group and 77.4% of those in the glipizide group had previously received antidiabetic treatment (a sulfonylurea for 90% of patients on sitagliptin and 93% of those on glipizide, metformin for 35.1% of patients on sitagliptin and 38.4% of those on glipizide, and an insulin for 5.5% of patients on sitagliptin and 3.7% of those on glipizide).
At inclusion, the mean HbA1c level was 7.8%, and 58.5% of the patients had a HbA1c level between 7 and 8%. The median level was 7.6%.
About 74% of the patients had moderate renal impairment and 26% had severe renal impairment. The renal impairment was due to diabetic nephropathy in 83% of cases.
27.4% of the patients on sitagliptin and 23.9% of the patients on glipizide had a history of cardiovascular disease.
The mean dose given to patients treated with glipizide was 7.5 mg. 27.4% of the patients in the glipizide group were given the maximum authorised dose of 20 mg/day.

[5] *Sitagliptin and glipizide were used at the optimal dosage recommended in their Marketing Authorisations. The threshold of non-inferiority used is that normally used in the evaluation of antidiabetics.*

Table 2: Characteristics of the patients included (per-protocol population)

	Sitagliptin group N = 135	Glipizide group N = 142
Age		
Mean (years)	64.8	64.3
< 55 years old n (%)	26 (19.3)	17 (12.0)
Between 55 and 64 years old n (%)	37 (27.4)	62 (43.7)
Between 65 and 74 years old n (%)	50 (37.0)	42 (29.6)
≥ 75 years old n (%)	22 (16.3)	21 (14.8)
Mean weight (kg)	68.0	70.2
Mean body mass index (kg/m²)	26.5	27.0
Severity of renal impairment		
Moderate n (%)	98 (72.6)	106 (74.6)
Severe n (%)	37 (27.4)	36 (25.4)
Mean HbA1c level (%)	7.8	7.8
Number (%) of patients with HbA1c levels at inclusion		
< 7%	7 (5.2)	6 (4.2)
≥ 7% and < 8%	80 (59.3)	82 (57.7)
≥ 8% and < 9%	42 (31.1)	48 (33.8)
≥ 9%	6 (4.4)	6 (4.2)
Mean fasting blood glucose level (mg/dl)	148.1	143.9
Mean duration of diabetes (years)	10.7	10.1
Oral antidiabetic treatment before inclusion		
yes n (%)	94 (69.6)	93 (65.5)
No n (%)	41 (30.4)	49 (34.5)

Primary efficacy endpoint:

Table 3: Change in HbA1c levels after 54 weeks in the per-protocol population:

Treatment group	N	Mean baseline HbA1c level (SD)	Mean in week 54 (SD)	Change by week 54 compared with baseline	
				Mean (SD)	LS mean (95% CI)
Sitagliptin	135	7.76 (0.65)	7.05 (0.74)	-0.70 (0.80)	-0.76 (-0.89. -0.62)
Glipizide	142	7.79 (0.70)	7.17 (0.80)	-0.62 (0.91)	-0.64 (-0.78. -0.51)
Estimated difference Sitagliptin *versus* glipizide				Difference between the LS means (95% CI) **-0.11 (-0.29, 0.06)**	

After 54 weeks of treatment, the difference between sitagliptin and glipizide in the per-protocol population in terms of the reduction in the HbA1c level was -0.11%, 95% CI [-0.29; 0.06]. As the upper limit of the confidence interval of this difference is less than the fixed threshold (0.4%), the non-inferiority of sitagliptin with respect to glipizide has been demonstrated.
This result was confirmed in the ITT population. The 54 week data were missing for about 32% of the patients included (33.2%, 70/211 of the patients in the sitagliptin group and 30.2%, 64/212 of the patients in the glipizide group).
It should be noted that sitagliptin was most effective up to the 42nd week of treatment. HbA1c levels rose after that point. For glipizide, the effect reached a maximum in the 18th week and was maintained after that.

Secondary endpoints:

- Mean change in the fasting blood glucose level:
  After 54 weeks of treatment, no difference was observed between the two treatment groups.

- Change in weight:
  In the per-protocol population, after 54 weeks of treatment, the average body weight had fallen by -0.6 kg 95% CI [-1.2; -0.0] in the sitagliptin group (n = 143) and increased by 1.2 kg 95% CI [0.6; 1.8] in the glipizide group (n = 148), which is a difference of -1.8 kg; 95% CI [-2.6; -1.0]; $p < 0.001$).

- Percentage of patients with an HbA1c level < 7%:
  The clinical target was achieved by 47.4% of the patients on sitagliptin (64/135) and 41.5% of the patients on glipizide (59/142).

3.1.2. Study P073

Aim and method: Randomised, double-blind, phase III study to evaluate the efficacy and safety of sitagliptin monotherapy at a dosage of 25 mg in patients with type 2 diabetes inadequately controlled by diet and exercise alone and end-stage renal disease treated by dialysis after 54 weeks of treatment.
There was also of group treated with glipizide in this study.

Inclusion in the study and randomisation was preceded by a washout phase during which the antidiabetic medication was discontinued diet and physical activity were optimised (for 14 weeks) followed by 2 weeks of single-blind placebo treatment.[6]

The protocol envisaged randomisation according to age (< 65 or ≥ 65 years old), cardiovascular disease history (with/without a history of cardiovascular, cerebrovascular, or peripheral vascular disease), history of cardiac failure (with/without).

Inclusion criteria:
Patients with type 2 diabetes, at least 30 years of age, with end-stage renal disease treated by haemodialysis or peritoneal dialysis for at least 6 months, inadequately controlled by diet and exercise alone (HbA1c level ≥ 7% and ≤ 9%) who have not received antidiabetic treatment for at least 3 months, or who are under treatment with antidiabetic monotherapy or low-dose dual therapy (dose ≤ 50% of the maximum recommended dose of each antidiabetic[7]) and with an HbA1c level ≥ 6.5% and ≤ 9%.

Principal exclusion criteria:
Identical to those in study P063, except treatment by dialysis.

Dosing regimen:
One hundred and twenty-nine (129) patients were randomised to receive:
- either sitagliptin at a dosage of 25 mg/day (n = 64)
- or glipizide at an initial dosage of 2.5 mg/day, which could be increased up to 20 mg/day (n = 65).[8]

[6] Patients not receiving antidiabetic treatment were able to start the single-blind placebo treatment phase immediately.
[7] These drugs were discontinued during the pre-inclusion phase.
[8] Patients with insufficient glycaemic control could be given insulin. To avoid an increase in the risk of hypoglycaemia, patients on glipizide discontinued their treatment once insulin treatment was initiated. Two patients on sitagliptin and four on glipizide had recourse to insulin.

Primary efficacy endpoint:
Mean change in HbA1c after 54 weeks of treatment compared to the baseline value for the sitagliptin treatment group.

The protocol envisaged the inclusion of 125 patients in each of the treatment groups in order to demonstrate a difference of 0.4% in respect of the variation in the HbA1c level with a power of 76% and an overall significance level of 0.05.

Analyses for the primary efficacy endpoint specified in the protocol were performed in sub-groups of patients (based on age, their blood glucose lowering treatment before inclusion, the initial HbA1c level, BMI, and the duration of diabetes). As no adjustment method was applied to take account of multiple comparisons, the possibility of an overestimation of the effect cannot be ruled out. Consequently, no conclusions can be drawn on the basis of these exploratory analyses, and they are therefore not presented.

Secondary endpoints after 54 weeks of treatment:
- mean change in the fasting blood glucose level in the sitagliptin group
- mean change in the HbA1c level in the two treatment groups
- percentage of patients with an HbA1c level < 6.5%.

Results:
The results were obtained from the analysis of all the randomised patients who received at least one dose of treatment (62/64 patients in the sitagliptin group, 59/65 patients in the glipizide group).

At inclusion, the characteristics of the patients in the two treatment groups were similar. They were:
- aged 59.5 on average (31% of patients were 65 or over),
- overweight (mean BMI of 27 kg/m^2).
They had had diabetes for 17.5 years on average.
Among the patients included, 73.4% of those in the sitagliptin group (47/64) and 81.5% of those in the glipizide group (53/65) had previously received antidiabetic treatment (a sulfonylurea for 89.4% of patients on sitagliptin and 98% of those on glipizide, metformin for 34% of patients on sitagliptin and 28% of those on glipizide, and an insulin for 23.4% of patients on sitagliptin and 24.5% of those on glipizide).
The average HbA1c level on inclusion was 7.8%. The majority of the patients (50.4%) had an HbA1c level between 7 and 8%. 34.4% of the patients had an HbA1c between 8 and 9%.
Among the randomised patients, 31.8% were on peritoneal dialysis and 68.2% were on haemodialysis. In 95% of the patients, the renal impairment was due to diabetic nephropathy.
69.8% of the patients included did not have a history of cardiovascular disease. Only 10.9% had cardiac failure.
The mean dose given to patients treated with glipizide was 5.3 mg. 12.3% of the patients in the glipizide group were given the maximum authorised dose of 20 mg/day.

Table 4: Characteristics of the patients included

	Sitagliptin group N = 64	Glipizide group N = 65
Age		
Mean (years)	60.5	58.5
< 55 years old n (%)	19 (29.7)	21 (32.3)
Between 55 and 64 years old n (%)	23 (35.9)	26 (40.0)
Between 65 and 74 years old n (%)	18 (28.1)	14 (21.5)
≥ 75 years old n (%)	4 (6.3)	4 (6.2)
Mean weight (kg)	69.8	68.2
Mean body mass index (kg/m²)	27.3	26.3
Peritoneal dialysis n (%)	18 (28.1)	23 (35.4)
Haemodialysis n (%)	46 (71.9)	42 (64.6)
Mean HbA1c level (%)	7.9	7.8
Number (%) of patients with HbA1c at inclusion		
< 7%	5 (7.8)	6 (9.2)
≥ 7% and < 8%	29 (45.3)	36 (55.4)
≥ 8% and < 9%	26 (40.6)	19 (29.2)
≥ 9%	4 (6.3)	3 (4.6)
Mean fasting blood glucose level (mg/dl)	159.2	166.0
Mean duration of diabetes (years)	18.6	16.6
Oral antidiabetic treatment before inclusion		
yes n (%)	24 (37.5)	31 (47.7)
No n (%)	40 (62.5)	34 (52.3)

Primary efficacy endpoint:

After 54 weeks of treatment, the observed change in the sitagliptin group compared with the baseline level was -0.72% 95% CI [-0.95; -0.48] $p < 0.001$.

It should be noted that the effect of sitagliptin reached a maximum in the 18th week of treatment. After that, the HbA1c level was stable up to the 36th week, then the effect declined.

Secondary endpoints:

- Mean change in the fasting blood glucose level:

After 54 weeks of treatment, a statistically significant reduction was observed in each treatment group (difference compared with the baseline value of -26.6 mg/dl 95% CI [-38.0; -15.3] $p < 0.001$ in the sitagliptin group, -31.2 mg/dl 95% CI [-42.6; -19.9] $p < 0.001$ in the glipizide group).

- Mean change in the HbA1c level in the two treatment groups:

After 54 weeks of treatment, the observed change in the glipizide group compared with the baseline level was -0.87 95% CI [-1.11; -0.63], $p < 0.001$.

There was no difference between sitagliptin and glipizide in terms of the reduction in the HbA1c level (between-group difference 0.15% 95% CI [-0.18; 0.49], NS).

- Percentage of patients with an HbA1c level < 6.5%:

The clinical target was achieved by 29% of the patients in the sitagliptin group (18/62) and 30.5% of the patients in the glipizide group (18/59).

3.2. Tolerance

3.2.1. Data obtained from study P063

There was at least one adverse event in 68.1% of the patients on sitagliptin (143/210) and 72.2% of the patients on glipizide (153/212). These events were due to treatment in 12.9% of the patients on sitagliptin (or 27 patients) and 18.4% of the patients on glipizide (39 patients).
The main adverse events were:

- infections in 24.8% of the patients on sitagliptin and 30.2% of the patients on glipizide
- gastrointestinal disorders in about 14% of patients (31 on sitagliptin, 30 on glipizide)
- metabolic and nutritional disorders in 14.8% of the patients in the sitagliptin group and 23.6% of the patients on glipizide
- nervous system disorders in 14.8% of patients on sitagliptin and 12.7% of patients on glipizide
- musculoskeletal and connective tissue disorders in 14.3% of patients on sitagliptin and 11.8% of patients on glipizide
- vascular disorders in 7.1% of the patients on sitagliptin and 6.1% of the patients on glipizide
- skin disorders in 7.1% of the patients on sitagliptin and 7.5% of the patients on glipizide
- tumours[9] in 6 patients in the sitagliptin group, none in the glipizide group.

Hypoglycaemia was reported by 6.2% of the patients on sitagliptin (13 patients,[10] 22 hypoglycaemic episodes) and 17% of the patients on glipizide (36 patients,[11] 93 hypoglycaemic episodes).

The number of patients who discontinued treatment on account of adverse events was 16 in the sitagliptin group and 17 in the glipizide group. These events were due to the treatment in five patients (three on sitagliptin, two on glipizide).

Two deaths were observed in each treatment group (sudden death in the sitagliptin group, death of cardiovascular origin in the glipizide group).
Two patients on sitagliptin and three on glipizide had myocardial infarctions. There was one case of unstable angina in the glipizide group.
One case of haemorrhagic stroke was observed in each group; two cases of ischaemic stroke were observed on sitagliptin and one on glipizide; and one transient ischaemic attack was observed on sitagliptin.
There were four cases of cardiac failure in the glipizide group, and none in the sitagliptin group.

3.2.2. Data obtained from study P073

There was at least one adverse event in 82.8% of the patients on sitagliptin (53/64) and 80% of the patients on glipizide (52/65). These events were due to treatment in 15.6% of the patients on sitagliptin (or 10 patients) and 20% of the patients on glipizide (13 patients).

[9] Eight patients under treatment with sitagliptin (six in study P063 and two in study P073) developed a tumour; these occurred in a variety of locations. In four cases, the cancerous nature of the tumour was confirmed. In the other four patients, the tumours were either benign or were not confirmed histologically. All these diagnoses were made less than 6 months after the start of treatment and the investigators did not consider that they were related to the treatment.
[10] Ten patients had a single hypoglycaemic episode and three reported two or more episodes.
[11] 17 patients had a single hypoglycaemic episode and 19 reported two or more episodes.

The main adverse events were:
- infections in 45.3% of the patients on sitagliptin (29/64) and 36.9% of the patients on glipizide (24/65)
- gastrointestinal disorders in 21.9% of the patients on sitagliptin and 24.6% of the patients on glipizide
- metabolic and nutritional disorders in 21.9% of the patients in the sitagliptin group and 24.6% of the patients on glipizide
- musculoskeletal and connective tissue disorders in 10.9% of patients on sitagliptin and 9.2% of patients on glipizide
- vascular disorders in 12.5% of the patients on sitagliptin and 15.4% of the patients on glipizide
- skin disorders in four patients on sitagliptin and seven on glipizide
- tumours[12] in two patients in the sitagliptin group, none in the glipizide group.

Hypoglycaemia was reported by 6.3% of the patients on sitagliptin (four patients,[13] seven hypoglycaemic episodes) and 10.8% of the patients on glipizide (seven patients,[14] 16 hypoglycaemic episodes).

After 54 weeks of treatment, the average body weight had fallen by -0.3 kg in the sitagliptin group (n = 45) and increased by 1.1 kg in the glipizide group (n = 41).

The number of patients who discontinued treatment on account of adverse events was seven in the sitagliptin group and eight in the glipizide group. These events were due to the treatment in three patients (one on sitagliptin, two on glipizide).

Deaths of cardiovascular origin occurred in two patients treated with sitagliptin and one treated with glipizide. There was one nonfatal cardiac arrest in each treatment group, one unstable angina in a patient on sitagliptin, a stroke in a patient on glipizide, and two cases of cardiac failure in each group.

3.2.3. Adverse effect data obtained from the latest PSUR (covering the period from 4 August 2009 to 3 August 2011)

Analysis of the data from the latest international PSUR for JANUVIA produced results in line with the risk information mentioned in the current Marketing Authorisation. Safety is closely monitored in the context of the international RMP.
It should be noted that, in addition to the European RMP for JANUVIA, Afssaps has set up an enhanced national pharmacovigilance monitoring programme, focusing mainly on monitoring infections, gastrointestinal disorders, rheumatological conditions and neuro-psychiatric disorders.
In total, 7496 reports of adverse events have been identified, including 1972 reports of serious cases. Twenty-seven of the 7496 reports were from studies and the other 7469 were spontaneous notifications by healthcare professionals.

The most frequently reported events were:
- gastrointestinal disorders, with a total of 1933 reports including 2488 events, mainly pancreatitis (459 events), nausea (268) and diarrhoea (244)
- skin and subcutaneous tissue disorders, with 1190 events, mainly skin rashes (317 cases), pruritis (178 cases) and urticaria (105 cases)
- metabolic and nutritional disorders, with 850 events, including hypoglycaemia (628 events), reduced appetite (78 events) and hyperglycaemia (38 events).

[12] Eight patients treated with sitagliptin (six in study P063 and two in study P073) developed a tumour; these occurred in a variety of locations. The cancerous nature of four of the tumours was confirmed. In the other four patients, the tumours were either benign or were not confirmed histologically. All these diagnoses were made less than 6 months after the start of treatment and the investigators did not consider that they were related to the treatment.
[13] Three patients had a single hypoglycaemic episode and one reported two or more episodes.
[14] Three patients had a single hypoglycaemic episode and four reported two or more episodes.

During this period, there were 1972 serious adverse event reports which described 3114 serious events that occurred under sitagliptin, including 459 cases of pancreatitis, 133 of acute pancreatitis, 127 overdoses, 165 cases of hypoglycaemia (90% of the hypoglycaemic events occurred in the presence of concomitant treatments – metformin, insulin, sulfonylureas – which are known to increase the risk of hypoglycaemia in patients treated with sitagliptin).

3.2.4. Post-Marketing Authorisation changes to the SPC of JANUVA 100 mg relating to safety (changes dated 26 November 2010 and 24 August 2011)

Since marketing, the SPC has been updated on account of the following additional adverse events that have been reported (frequency not known): hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, **cutaneous vasculitis** and exfoliative skin lesions including Stevens-Johnson syndrome, **pancreatitis**, arthralgia and myalgia.
The information summarized by the EMA for some of these events is as follows:

- Pancreatitis:
  The number of reports in the clinical studies was very low. Since the marketing of sitagliptin, 108 cases of (acute) pancreatitis have been reported, 38 of which were insufficiently documented. In the two fatal cases reported, several comorbidities and concomitant treatments were confounding factors. On the basis of the available data, it is not possible to exclude a causal relationship between the drug and the effect.
- Cutaneous vasculitis:
  A total of 15 cases have been reported (spontaneous notifications or during clinical studies) with a number of confounding factors in the majority of cases. Because hypersensitivity reactions are among the known effects of sitagliptin and one case of vasculitis was positive after reintroduction of sitagliptin, a causal relationship is considered probable.

3.3. Conclusion

The use of sitagliptin in patients with type 2 diabetes and RI has been evaluated in two studies.

One randomised, double-blind, non-inferiority study (P063) compared monotherapy with sitagliptin and glipizide in 426 patients with type 2 diabetes inadequately controlled by diet and exercise alone and with moderate to severe RI.
The patients were on average 64.6 years old, overweight, with a mean HbA1c level of 7.8% (which corresponds to mild diabetes), 67.5% of them had already been given an antidiabetic treatment and 74% had moderate RI. Sitagliptin was administered at a dosage of 25 mg/day in patients with severe RI and 50 mg/day in patients with moderate RI.
After 54 weeks of treatment:

- the non-inferiority of sitagliptin with respect to glipizide was demonstrated. In the per-protocol population, the difference between sitagliptin and glipizide in terms of the reduction in the HbA1c level was -0.11% 95% CI [-0.29; 0.06]; that is, the upper limit of the confidence interval for this difference is less than the fixed threshold (0.4%). This result was confirmed in the ITT population.
- an HbA1c level < 7% (clinical objective evaluated as a secondary endpoint) was achieved by 47.4% of the patients on sitagliptin (64/135) and 41.5% of the patients on glipizide (59/142).

The second controlled, randomised, double-blind study (P073) versus glipizide, the objective of which was to evaluate sitagliptin monotherapy at a dose of 25 mg/day, was carried out in 129 patients with type 2 diabetes inadequately controlled by diet and exercise alone and with end-stage renal disease; the patients were 59.5 years old, overweight, with a baseline HbA1c level of 7.8% (which corresponds to mild diabetes), and more than 70% of them had already been given antidiabetic treatment.
The primary efficacy endpoint, the mean change in the HbA1c level after 54 weeks of treatment, was only evaluated in the sitagliptin group. This before/after treatment comparison is not very relevant.

The protocol envisaged comparison of the sitagliptin and glipizide groups in respect of the change in the HbA1c level as a secondary efficacy endpoint. No difference between the two groups was demonstrated.

The safety profile of 25 mg and of 50 mg of sitagliptin does not appear to be different from that of the 100 mg dose. The principal adverse events were infections, gastrointestinal disorders, musculoskeletal disorders and hypoglycaemia, were more numerous on glipizide than on sitagliptin.
Since the marketing of proprietary medicinal products containing sitagliptin, the SPC has been updated because new serious adverse events have been reported (frequency not known): hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis and exfoliative skin lesions including Stevens-Johnson syndrome, pancreatitis, arthralgia and myalgia.

3.4. Comments

In the two studies, sitagliptin was evaluated as monotherapy in combination with diet and physical exercise. In this indication, the efficacy of JANUVIA has been demonstrated in a non-inferiority study versus glipizide. The choice of this sulfonylurea, despite the low number of prescriptions in France, could be justified because it causes fewer hypoglycaemic episodes in patients with renal impairment than other sulfonylureas, as its metabolite is only very weakly active or inactive.

Sitagliptin has mainly been evaluated in patients with moderate RI or end-stage renal disease treated by dialysis, with few patients with severe RI having been evaluated.

There are no clinical data on dual therapy in combination with a sulfonylurea or an insulin.
Data are available in these indications for a dosage of 100 mg/day. In combination with a sulfonylurea, the role of sitagliptin 100 mg/day + sulfonylurea is limited, in view of the very modest efficacy in respect of the reduction in the HbA1c level.
According to the guidelines[15, 16] and the data in the literature,[17] when insulin therapy is initiated to maintain or improve control of the blood glucose level, the following dual therapies have been validated: insulin + metformin or insulin + sulfonylurea. In case of renal impairment, only the insulin + sulfonylurea combination is justified. On the basis of the available data, the TC considers that dual therapy with insulin + sitagliptin at a dose of 100 mg cannot be recommended.

Few patients with a history of cardiovascular disease were included in the two studies, even though this comorbidity is common in patients with renal impairment.

[15] Scottish Intercollegiate Guidelines Network SIGN; 2010, Management of diabetes. A national clinical guideline. March 2010. *http://www.sign.ac.uk/pdf/sign116.pdf*
[16] Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R*, et al.* Medical management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care, January 2009, Vol 32 (1): 193-203.
[17] Hemmingsen B, Christensen LL, Wetterslev J, Vaag A, Gluud C, Lund SS, Almdal T. Comparison of metformin and insulin versus insulin alone for type 2 diabetes: systematic review of randomised clinical trials with meta-analyses and trial sequential analyses. BMJ. 2012 Apr 19; 344: e1771. doi: 10.1136/bmj.e1771.

It is emphasised that, for the comparators (ONGLYZA 2.5 mg, TRAJENTA), the Committee is only in possession of studies versus placebo with numerous methodological limitations.

TRAJENTA (linagliptin) has been evaluated in monotherapy in its indication in cases in which metformin is not tolerated or contraindicated due to RI in a randomised, double-blind, phase III study versus placebo in 227 patients, 93% of whom showed intolerance to metformin, and which was of short duration (18 weeks). Metformin was only contraindicated due to RI in 7% of the patients. The TC considered, in particular, that the available data in cases of renal impairment were very limited, bearing in mind the very small number of patients with renal impairment evaluated and the absence of data versus an active comparator, in particular a sulfonylurea, which led to the classification of the AB of this proprietary medicinal product as insufficient in its opinion of 20 June 2012. In another double-blind, randomised, placebo-controlled study performed in 133 patients with renal failure (severe in 92.6% of patients from the linagliptin group and 78.5% of patients from the placebo group) the reduction in HbA1c value was greater with linagliptin than with placebo after 12 weeks of treatment (difference of -0.59 ± 0.15%; 95% CI [-0.88; -0.29] p < 0.0001). The level of responders was low (clinical endpoint, HbA1c level < 7%, achieved by 18.2% of the patients in the linagliptin group and 9.7% of the patients in the placebo group). However, these results were not used by the Committee to evaluate the efficacy of linigliptin in patients with renal impairment for the following reasons: the majority of the patients were treated with insulin and/or a sulfonylurea although linagliptin is not indicated in combination with these treatments, the efficacy was only measured for 12 weeks, only a small number of patients were evaluated, there were numerous discontinuations of treatment, and patients with a history of cardiovascular disease were excluded from the study.
ONGLYZA (saxagliptin) was evaluated in a randomised, double-blind, phase III study versus placebo in combination with continuation of diet and lifestyle measures and the previous antidiabetic treatment in 170 patients displaying inadequate control (HbA1c level > 8%) and moderate RI in the case of 52.9% of the patients. The analysis of this study and its results lead the TC to classify the AB of this proprietary medicinal product in the treatment of patients with diabetes and renal impairment as insufficient, in view of the small number of patients included, the short duration of the study (12 weeks), the low efficacy versus placebo (difference of -0.42%, 95% CI [-0.71; -0.12], p = 0.007 in terms of the reduction in the HbA1c level), the limited data in severe RI (low number of patients), and because the majority of patients (83.5%) were treated with insulin (although saxagliptin is not indicated in combination with insulin).

Furthermore, the number of patients on sitagliptin who have been evaluated is larger than the number on the comparators.

No studies have demonstrated the superiority of sitagliptin over the reference treatments in the indications shown in the Marketing Authorisation.[18]
There are no morbidity and mortality data but a study is underway (TECOS).

[18] T. Karagiannis et 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.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Type 2 diabetes is a chronic disease with potentially serious complications, particularly cardiovascular complications. The renal impairment observed in patients with diabetes is most often due to microvascular complications in the course of the disease. It may also be aggravated by the associated macroangiopathy that may be present.

The objective of the treatment of patients with type 2 diabetes and renal impairment is to reduce morbidity and mortality due to type 2 diabetes by controlling the blood glucose level and by controlling the associated cardiovascular risk. A poorly controlled blood glucose level is a risk factor for the progression or the renal disease.

The proprietary medicinal product JANUVIA, at dosages of 25 and 50 mg, would be used as a treatment for hyperglycaemia in patients with moderate, severe or end-stage renal disease.

4.1.1. In monotherapy

The available data (non-inferiority study versus sulfonylurea, the reference treatment because it is the first-line treatment in monotherapy in renal impairment) are at an acceptable level of evidence compared with those available for other gliptins, for which there are only studies against placebo with numerous methodological limitations.
The efficacy/adverse effects ratio for these medicinal product is low.
The risks relating, in particular, to the occurrence of pancreatitis and allergic reactions, are poorly understood in the long term.

Taking into account the results of the non-inferiority study versus glipizide and the limited number of alternative treatments, sitagliptin, at a dosage of 50 mg, may be suggested to patients with type 2 diabetes and moderate RI, particularly when sulfonylureas are contraindicated and before resorting to insulin treatment.
Sitagliptin at a dosage of 25 mg, despite the low level of evidence in the available data and in view of the limited number of alternative treatments, may be suggested to patients with type 2 diabetes and severe or end-stage renal disease, before resorting to insulin treatment.

There are alternative drugs to this proprietary medicinal product in the management of diabetic patients; these are predominantly sulfonylureas and insulin in patients with moderate RI, and insulin in patients with severe RI.

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 renal impairment with an indication for JANUVIA 25 mg or 50 mg 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.[19] 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 limited number of alternative treatments, particularly in cases of moderate or severe renal impairment, the availability of these two forms, 50 mg and 25 mg, for patients with moderate to severe renal impairment or end-stage renal disease respectively, might address an identified public health need.

[19] 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 chronic diseases 2007-2011

However, the methodological limits of the clinical study carried out using monotherapy in patients with renal impairment makes the results difficult to interpret in terms of the supplementary impact on the control of the blood glucose level. Moreover, the available data do not make it possible to estimate the impact of JANUVIA 25 mg and 50 mg on morbidity and mortality and quality of life of patients with type 2 diabetes.
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 in terms of safety, the course of the renal impairment, and the control of the blood glucose level in particular.
In the current state of knowledge, it is impossible to reach any conclusions as to how JANUVIA 25 mg and 50 mg might meet the identified public health need.
Consequently, it is not expected that monotherapy with the proprietary medicinal products JANUVIA 25 mg and 50 mg will benefit public health in cases of renal impairment in the indications in patients with type 2 diabetes.

Consequently, the actual benefit of the proprietary medicinal products JANUVIA 25 mg and 50 mg is low.

4.1.2. In dual therapy, in combination with a sulfonylurea

No data are available. However, in case of moderate RI and the immediate initiation of dual therapy because of poor control of the blood glucose level and contraindication to metformin due to renal failure, the combination sitagliptin 50 mg + sulfonylurea could be considered in patients with moderate RI before resorting to insulin treatment. The principal alternative treatment is the combination insulin + sulfonylurea.
If moderate renal impairment develops in patients already treated and stabilised on sitagliptin at a dosage of 100 mg in combination with a sulfonylurea, the dose of sitagliptin can be reduced to 50 mg.

The efficacy/adverse effects ratio for this medicinal product is low.
The risks relating, in particular, to the occurrence of pancreatitis and allergic reactions, are poorly understood in the long term.
There are alternative drugs to this proprietary medicinal product for the management of diabetic patients with moderate renal impairment.

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 renal impairment with an indication for JANUVIA 50 mg 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.[19] 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 limited number of alternative treatments, particularly in cases of moderate or severe renal impairment, the availability of the 50 mg form for patients with moderate renal impairment might address an identified public health need.
However, in the absence of clinical data relating to this dosage in combination with a sulfonylurea, the additional impact of this dosage on the control of the blood glucose level is difficult to quantify. Moreover, the available data do not make it possible to estimate the impact of JANUVIA 50 mg on morbidity and mortality and quality of life of patients with type 2 diabetes.
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 in terms of safety, the course of the renal impairment, and the control of the blood glucose level in particular.
In the current state of knowledge, it is impossible to reach any conclusions as to how JANUVIA might meet the identified public health need.

Consequently, it is not expected that monotherapy with the proprietary medicinal product JANUVIA 50 mg in combination with a sulfonylurea will benefit public health in cases of renal impairment in the indications in patients with type 2 diabetes.

Consequently, the actual benefit of the proprietary medicinal product JANUVIA at a dose of 50 mg is moderate.

4.1.3. In dual therapy in combination with insulin

No data are available. However, in cases of moderate RI, the principal alternative treatment is the combination insulin + sulfonylurea. In cases where sulfonylureas are contraindicated, dual therapy with insulin + sitagliptin at a dosage of 50 mg from the outset is a possible strategy.
In cases of severe renal impairment or end-stage renal disease, dual therapy with insulin + sitagliptin at a dosage of 25 mg is a possible alternative to insulin on its own or the combination insulin + glinide.
In the case of progression to renal impairment, the combination of low-dose sitagliptin (25 mg or 50 mg) with insulin following treatment with 100 mg is not indicated, as the combination of sitagliptin 100 mg and insulin is not recommended.

The efficacy/adverse effects ratio for these medicinal products is low.
The risks relating, in particular, to the occurrence of pancreatitis and allergic reactions, are poorly understood in the long term.
There are alternative drugs to this proprietary medicinal product for the management of diabetic patients with moderate, severe or end-stage renal disease.

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 renal impairment with an indication for JANUVIA 25 mg or 50 mg 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.[19] 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 limited number of alternative treatments available, particularly in cases of moderate or severe renal impairment, the availability of these two forms, 50 mg and 25 mg, for patients with moderate to severe renal impairment or end-stage renal disease respectively, might address an identified public health need.
However, in the absence of clinical data relating to these dosages in combination with insulin, the additional impact of these dosages on the control of the blood glucose level is difficult to quantify. Moreover, the available data do not make it possible to estimate the impact of JANUVIA 25 mg and 50 mg on morbidity and mortality and quality of life of patients with type 2 diabetes.

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 in terms of safety, the course of the renal impairment, and the control of the blood glucose level in particular.
In the current state of knowledge, it is impossible to reach any conclusions as to how JANUVIA 25 mg and 50 mg might meet the identified public health need.

Consequently, it is not expected the proprietary medicinal products JANUVIA 25 mg et 50 mg in combination with insulin will benefit public health in cases of renal impairment in the indications in patients with type 2 diabetes.

Consequently, the actual benefit of the proprietary medicinal products JANUVIA 25 mg and

50 mg is moderate.

4.1.4. In the indications in combination with metformin

The Marketing Authorisation has been validated in situations that do not conform with the SPC of the medicinal products.
The indications for sitagliptin at the dosages of 25 mg and 50 mg recommended for diabetic patients with moderate, severe or end-stage renal disease in combination with metformin do not exist in practice, since metformin is contraindicated in renal impairment.
Thus, the Committee considers that the actual benefit of the proprietary medicinal products JANUVIA at dosages of 25 mg and 50 mg in their indications combination with metformin, in dual therapy and triple therapy, is insufficient to justify reimbursement by National Health Insurance.

4.2. Improvement in actual benefit

In view of the available data, the Transparency Committee considers that the proprietary medicinal products JANUVIA at dosages of 25 mg and 50 mg of sitagliptin, in monotherapy or in dual therapy in combination with a sulfonylurea or insulin, offer no improvement in actual benefit (IAB V) in the treatment of diabetic patients with renal impairment.

4.3. Therapeutic use

The aim of treatment is control of the blood glucose level, 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 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 to combat a sedentary lifestyle and encourage a balanced diet are essential interventions at all stages of diabetes management.
According to the most recent guidelines from of the ADA and EASD,[20] adaptation of the dosage is required as soon as renal function is impaired.

In patients with renal impairment, metformin is contraindicated if the glomerular filtration rate is < 60 ml/min and the main treatments recommended are sulfonylureas or insulin, if the renal impairment is moderate (clearance between 30 and 50 ml/min), and insulin in cases of severe renal impairment (clearance < 30 ml/min). In the event of failure of properly conducted monotherapy using drugs that have been proved to be effective, a change to dual therapy should be considered.

Therapeutic use of JANUVIA 25 mg and JANUVIA 50 mg
In monotherapy, sitagliptin at a dosage of 50 mg could be an alternative in patients with type 2 diabetes and moderate RI, particularly where sulfonylureas are contraindicated and before resorting to insulin treatment.
Sitagliptin at a dosage of 25 mg could be suggested as monotherapy in patients with type 2 diabetes and severe RI or end-stage renal disease before resorting to insulin treatment.

[20] 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.

In the other indications, these dosages would permit the continuation of treatment with sitagliptin in patients treated with a 100 mg dosage but in whom changes in the renal function require a dosage reduction. They can also be prescribed from the start in patients with renal impairment who were not previously treated with sitagliptin 100 mg.

- Thus, in patients with moderate RI, the combination sitagliptin 50 mg/sulfonylurea could be considered before resorting to insulin treatment. In cases where sulfonylureas are contraindicated, dual therapy with insulin + sitagliptin at a dosage of 50 mg from the outset is possible.
  If moderate renal impairment develops in patients already treated and stabilized on sitagliptin at dosage of 100 mg in combination with a sulfonylurea, the dose of sitagliptin must be reduced to 50 mg.

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

- In the case of progression to renal impairment, there is no therapeutic use for the combination insulin/sitagliptin 25 mg or 50 mg after high-dose treatment (100 mg) with sitagliptin combined with insulin in any stage of renal impairment.

4.4. Target population

A retrospective observational study was carried out on the basis of the LPD study[21] between 1 January and 31 December 2010 in a sample of 52,819 patients with type 2 diabetes.
Of these patients, 12,819 were both on antidiabetic treatment and had a reported value for creatinine clearance: 17.3% had chronic renal impairment, 1.2% had severe renal impairment and 0.4% had end-stage renal disease.

[21] Which includes the medical records of more than 2.6 million patients who consulted a representative sample of 1200 general practitioners

Table 5: Distribution of patients with type 2 diabetes and moderate, severe or end-stage renal disease as a function of their antidiabetic treatment.

Populations considered	Raw data n (%)
Treated T2D patients with moderate renal impairment	**2,224**
Monotherapy	
• OAD±GLP1	1181 (53.1%)
o *Metformin alone*	*575 (48.7%)*
o *Sulfonylurea alone*	*385 (32.6%)*
o *Glinide alone*	*120 (10.2%)*
o *Another pharmacological class*	*101 (8.5%)*
• Insulin	201 (9.0%)
Dual therapy	
• OAD±GLP1	528 (23.7%)
o *Sulfonylurea and metformin*	*244 (46.2%)*
o *Sulfonylurea and another pharmacological class*	*47 (8.9%)*
o *2 other pharmacological classes*	*179 (33.9%)*
• Including an insulin	133 (6.0%)
Treated T2D patients with severe renal impairment	**151**
Monotherapy	
• OAD±GLP1	64 (42.4%)
o *Sulfonylurea alone*	*21 (32.8%)*
o *Glinide alone*	*17 (26.6%)*
o *Metformin alone*	*13 (20.3%)*
o *Another pharmacological class*	*13 (20.3%)*
• Including an insulin	40 (26.5%)
Dual therapy	
• Including an insulin	17 (11.3%)
Treated T2D patients with end-stage renal disease	**52**
Monotherapy	
• OAD±GLP1	35 (67.3%)
o *Metformin alone*	*18 (51.4%)*
o *Sulfonylurea alone*	*9 (25.7%)*
o *Another pharmacological class*	*8 (22.9%)*
• Insulin	2 (3.8%)
Dual therapy	
• Including an insulin	3 (5.8%)

The ENTRED [Representative national sample of the diabetic population] study surveyed 2,665,100 patients with type 2 diabetes who were treated with antidiabetics. On the basis of these data, application of the raw data from the LPD study and the therapeutic strategy described, it is possible to determine the number of patients with type 2 diabetes and moderate, severe or end-stage renal disease (a total of around 504,000 patients) and to subdivide them according to the type of treatment.

- The number of treated patients with type 2 diabetes and moderate renal impairment is estimated at 461,060. Of these patients:
  - 53% are treated with monotherapy, 32.6% of them with a sulfonylurea alone (that is, 165,000 patients) and 9% are treated by insulin monotherapy (41,500 patients)
  - 23.7% are treated with dual therapy with an OAD in 46.2% of cases and an insulin in 6% of cases (that is, 78,148 patients).

- The number of treated patients with type 2 diabetes and severe renal impairment is estimated at 31,980. Of these patients:
    - 42% are treated with monotherapy with an oral antidiabetic (13,560 patients)
    - 11.3% are treated with dual therapy including insulin (3614 patients).

- The number of treated patients with type 2 diabetes and end-stage renal disease treated by dialysis is estimated at 10,660. Of these patients:
    - 67% are treated with monotherapy with an oral antidiabetic (7174 patients)
    - 5.8% are treated with dual therapy including insulin (618 patients).

In total, the target population of JANUVIA 50 mg and JANUVIA 25 mg would be of the order of 309,000 patients.

4.5. Transparency Committee recommendations

- In the indications for combination with metformin, in dual therapy and triple therapy:

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 for monotherapy and dual therapy in combination with a sulfonylurea or insulin:

The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance (B/28) and on the list of medicines approved for hospital use and various public services (B/28 and B/50) in the dosages given in the Marketing Authorisation.

Packaging: not appropriate for the prescription conditions
Packaging in boxes of 30, 60 and 90 tablets would be more appropriate.