HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

18 July 2012

JANUVIA 100 mg, film-coated tablets
B/28 (CIP code: 379 250-4)
B/50 (CIP code: 570 745-4)
sitagliptin
List I
ATC Code: A10BH01 (DPP-4 inhibitor, or gliptin)
Date of MA (centralised procedure): 21 March 2007

JANUMET 50 mg/1000 mg, film-coated tablet
B/56 (CIP code: 386 781-1)
B/50 (CIP code: 573 121-1)
sitagliptin/metformin
List I
ATC Code: A10BD07 (combination of oral antidiabetic agents)
Date of MA (centralised procedure) 16 July 2008

Applicants: MERCK SHARP & DOHME-CHIBRET

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) in the following extensions of indication for JANUVIA:
"For 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 contraindications or intolerance.
- as an add-on to insulin (with or without metformin) when diet and exercise plus stable dose of insulin do not provide adequate glycaemic control." (date of extensions of indication: 9 November 2009 – centralised procedure)

Inclusion on the list of medicines refundable by National Health Insurance (B/56) and approved for hospital use (B/56 and B/50) in the following extensions of indication for JANUMET:
"JANUMET is indicated as an adjunct to diet and exercise to improve glycaemic control in type 2 diabetic patients
- as an add-on to insulin (triple therapy) when stable doses of insulin and metformin alone do not provide adequate glycaemic control" (date of extension of indication: 28 October 2009 – centralised procedure)

The companies are only requesting inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use for the indication in combination with insulin. The transparency Committee, however, has decided to produce a review for all of the extensions to indications for the correct use of the medicine in the management of type 2 diabetic patients.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredients

Sitagliptin for JANUVIA
Sitagliptin/metformin for JANUMET

1.2. Indications

For JANUVIA
"For 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 contraindications or intolerance.**

As dual oral therapy in combination
- with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control. *(Indication already evaluated by the TC - cf opinion of 6 June 2007)*
- with a sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance. *(Indication already evaluated by the TC - cf opinion of 24 June 2009)*
- with 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 *(Indication already evaluated by the TC - cf opinion of 6 June 2007, although obsolete as glitazones are no longer available in France).*

As triple oral therapy in combination:
- with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. *(indication already evaluated by the TC cf opinion of 24 June 2009)*
- with a PPARγ receptor agonist and metformin, when the PPARγ receptor agonist is appropriate and dual therapy with these two medicines combined with diet and physical exercise does not achieve adequate glycaemic control *(This indication cannot be evaluated 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 a stable dose of insulin combined with diet and physical exercise does not provide adequate glycaemic control."

For JANUMET
"For patients with type 2 diabetes mellitus, JANUMET is indicated as an adjunct to diet and exercise to improve glycaemic control:

- in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin. (Indication already evaluated by the TC - cf opinion of 29 April 2009)

- in combination with a sulphonylurea (i.e., triple combination therapy) in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea. (Indication already evaluated by the TC - cf opinion of 29 April 2009)

- as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist. (This indication cannot be evaluated by the TC as the glitazones are no longer available in France)

- **JANUVIA is also indicated as add-on to insulin (i.e., triple combination therapy) when stable dose of insulin and metformin alone do not provide adequate glycaemic control."**

1.3. Dosage

For JANUVIA
"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 sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia (see section 4.4 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.

Renal impairment
When considering the use of sitagliptin in combination with another anti-diabetic product, its conditions 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 (ESRD) 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.

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

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

For JANUMET in the extension to indication being examined
The dose of antihyperglycaemic therapy with JANUVIA should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin.

For patients inadequately controlled with insulin and the maximal tolerated dose of metformin
The dose of JANUMET should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When JANUMET is used in combination with insulin a lower dose of insulin may be required to reduce the risk of hypoglycaemia (see section 4.4 of the SPC).
All patients must continue their diet dividing their intake of carbohydrates regularly during the day. Overweight patients must continue their reduced calorie diet.

Special populations
Renal impairment
JANUMET should not be used in patients with moderate or severe renal impairment (creatinine clearance < 60 ml/min) (see sections 4.3 and 4.4 of the SPC).

Hepatic impairment
JANUMET should not be used in patients with hepatic impairment (see sections 4.3 and 5.2 of the SPC).

Elderly
As metformin and sitagliptin are excreted by the kidney, JANUMET should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly (see sections 4.3 and 4.4 of the SPC). Limited safety data on sitagliptin is available in patients > 75 years of age and care should be exercised.

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

Method of administration
JANUMET should be given twice daily with meals to reduce the gastrointestinal undesirable effects associated with metformin."

1.4. Warnings and precautions for use (cf 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 medicinal products not known to cause hypoglycaemia (for example, metformin), rates of hypoglycaemia reported with sitagliptin were similar to rates in patients taking placebo. When sitagliptin was added to a sulphonylurea or to insulin, the incidence of hypoglycaemia was increased over that of placebo. **Therefore, to reduce the risk of hypoglycaemia, a lower dose of sulphonylurea 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 and severe renal impairment, as well as in end stage renal disease patients requiring haemodialysis or peritoneal dialysis (see sections 4.2 and 5.2).
When considering the use of sitagliptin in combination with another anti-diabetic product, its conditions for use in patients with renal impairment should be checked.

Hypersensitivity reactions
Post-marketing reports of serious hypersensitivity reactions in patients treated with JANUVIA have been reported. **These reactions include anaphylaxis, angioedema, and exfoliating skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with JANUVIA,** with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue

JANUVIA, assess for other potential causes for the event, and institute alternative treatment for diabetes."

Pancreatitis

In post-marketing 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 suspected medicinal products should be discontinued.

These warnings are found in the JANUMET SPC.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2012)

A	Gastrointestinal tract and metabolism
A10	Diabetic medicines
A10B	Antidiabetic agents, excluding insulin
A10BH	dipeptidylpeptidase-4 (DPP-4) inhibitors
A10BH01	sitagliptin

A :	Gastrointestinal tract and metabolism
A10:	Medicines for diabetes
A10B:	Anti-diabetic agents, excluding insulin
A10BD:	Combination of oral antidiabetic agents
A10BD07:	sitagliptin/metformin

2.2. Medicines in the same therapeutic category

- Another gliptin has Marketing Authorisation indication as monotherapy.
  This is linagliptin (TRAJENTA) indicated for use "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." *(insufficient AB declared by the Committee in its opinion of 20 June 2012)*

- -No other gliptin has an MA indication for combination with insulin to date.

2.3. Medicines with a similar therapeutic aim

- <u>as monotherapy:</u>
  - metformin
  - sulphonylureas
  - repaglinide
  - intestinal alpha-glucosidase inhibitors

- <u>in combination with insulin</u>:
  - metformin
  - sulphonylureas
  - injectable incretin mimetic (exenatide[1])

[1] BYETTA (exenatide) was approved by the CHMP for the following extension of indication on 16 February 2012: "BYETTA is also indicated for use in combination with basal insulin or with or without metformin and/or pioglitazone in adults who have not achieved adequate glycaemic control with these medicines."

3. ANALYSIS OF AVAILABLE DATA

The applicant submitted:
- a randomised, double-blind, phase III, non-inferiority study (study P049[2]), which compared sitagliptin with metformin,
- a double-blind, randomised, placebo-controlled, phase III study (study P051[3]), which examined sitagliptin in combination with insulin therapy, with or without metformin, in patients inadequately controlled with stable dose insulin.

3.1. Efficacy results

3.1.1. Monotherapy study (study P049)

Objective and methodology: double-blind, randomised, phase III study to demonstrate non-inferiority of sitagliptin monotherapy to metformin, in type 2 diabetic patients inadequately controlled with diet and physical exercise alone after treatment for 24 weeks.

Inclusion criteria:
Type 2 diabetic patients at least 18 years old who were inadequately controlled (HbA1c ≥ 6.5% and ≤ 9%) with diet and physical exercise and who had not received any diabetic treatment for at least 4 months.

Method of administration
1050 patients were randomised to:
- either sitagliptin at a dosage of 100 mg/day (n=528)
- or metformin at an initial dosage of 500 mg/day which was increased up to 1,000 mg twice daily over a maximum period of 5 weeks[4] (n=522).

All patients were required to follow the recommended diet and physical exercise programme throughout the study.

Primary efficacy endpoint:
Mean change in HbA1c at 24 weeks' treatment compared with the baseline value.
Sitagliptin was deemed to be non-inferior to metformin if the upper limit of the 95% confidence interval of the difference in HbA1c levels between the two treatments (sitagliptin – metformin) was less than 0.4%.[5]

Main secondary efficacy endpoint after treatment for 24 weeks:
- percentage of patients with HbA1c <6.5%

Results:

The patient characteristics were similar at inclusion in both treatment groups. Average patient age was 56 years old, and the majority was obese (mean BMI 30.8 kg/m^2).
The diabetes had been present for an average of 12.4 ± 6.6 years.

Mean HbA1c on inclusion was 7.2 ± 0.7%.
93.7% of patients randomised received a dose of 2000 mg of metformin.

[2] Aschner P, Katzeff H, Guo H, et al. Efficacy and safety of monotherapy of sitagliptin compared with metformin in patients with type 2 diabetes. Diabetes Obes Metab 2010; 12: 252-261.
[3] Vilsbøll T, Rosenstock J, Yki-Järvinen H, et al. Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes. Diabetes Obes Metab 2010 Feb; 12: 167-77.
[4] The dose of metformin was reduced to 1000 mg/day if it was not tolerated.
[5] Sitagliptin and metformin were used at the optimal dosage recommended in their MA. The non-inferiority threshold used was the standard threshold in evaluating antidiabetic agents.

Table 1: characteristics of patients included (Per Protocol population)

Age (years)				
Treatment group	N	Mean + SD	Median	Range
Sitagliptin	455	56.3 + 10.7	57.0	20.0 to 78.0
Metformin	439	55.7 + 10.3	56.0	28.0 to 78.0
Global	894	56.0 + 10.5	57.0	20.0 to 78.0
Body mass index (kg/m²)				
	N	Mean + SD	Median	Range
Sitagliptin	455	30.7 + 4.7	30.5	20.3 to 40.0
Metformin	437	30.9 + 4.9	30.6	20.3 to 40.6
Global	892	30.8 + 4.8	30.5	20.3 to 40.6
HbA1c (%)				
	N	Mean + SD	Median	Range
Sitagliptin	455	7.2 + 0.7	7.1	5.7 to 10.4
Metformin	439	7.2 + 0.7	7.1	5.6 to 10.1
Global	894	7.2 + 0.7	7.1	5.6 to 10.4
HbA1c distribution				
	N	Number (%) of patients with HbA1c at inclusion		
		<7%	≥ 7 and <8%	≥ 8%
Sitagliptin	455	199 (43.7)	182 (40.0)	74 (16.3)
Metformin	439	182 (41.5)	184 (41.9)	73 (16.6)
Global	894	381 (42.6)	366 (40.9)	147 (16.4)
Fasting blood glucose (mg/dL)				
	N	Mean + SD	Median	Range
Sitagliptin	453	142.4 + 31.9	136.0	46.0 to 267.0
Metformin	436	141.9 + 33.1	135.0	63.0 to 319.0
Global	889	142.2 + 32.5	136.0	46.0 to 319.0
Time since diagnosis of type 2 diabetes (years)				
	N	Mean + SD	Median	Range
Sitagliptin	455	2.6 + 3.9	1.0	0.0 to 27.0
Metformin	439	2.1 + 3.5	0.9	0.0 to 30.0
Global	894	2.4 + 3.7	1.0	0.0 to 30.0

Primary efficacy endpoint:

Table 2: change in HbA1c at 24 weeks in the Per Protocol population :

Treatment group	N	Mean baseline HbA1c (SD)	Mean at 24 weeks (SD)	Change at week 24 compared to baseline.	
				Mean (SD)	Mean MC (95% CI) †
Sitagliptin	455	7.22 (0.73)	6.80 (0.71)	-0.42 (0.03)	-0.43 (-0.48, -0.38)
Metformin	439	7.25 (0.69)	6.68 (0.62)	-0.57 (0.03)	-0.57 (-0.62, -0.51)
Estimated difference Sitagliptin *versus* metformin				Mean difference in MC (95% CI): **0.14 (0.06, 0.21)**	

The difference in HbA1c reduction between sitagliptin and metformin in the per protocol population after 24 weeks treatment was 0.14%, 95% CI [0.06; 0.21]. The upper limit of the confidence interval of this difference was below the fixed threshold (0.4%) and sitagliptin was therefore demonstrated to be non-inferior to metformin.

This result was confirmed in the ITT population.

It should be noted that the effect of sitagliptin was greatest up to the 12th week of treatment. Beyond that, HbA1c levels rose although continued to fall in the metformin group.

Primary efficacy endpoint:
The treatment goal (HbA1c <6.5%) was achieved by 33.6% of patients on sitagliptin (153/455) and by 39.2% of patients on metformin (172/439).

3.1.2. Study in combination with insulin with or without metformin (study P051)

Objective and methodology: This was a double-blind, randomised, phase III study, the aim of which was to compare the efficacy and safety of the insulin + sitagliptin combination to that of the insulin +placebo combination (with or without metformin) after 24 weeks of treatment.

The protocol stratified randomisation according to whether or not metformin was being received concomitantly, the type of insulin received (insulin mix[6] or intermediary/slow acting insulin) and whether or not a test meal was given to evaluate insulin resistance indices.

Inclusion criteria:
Type 2 diabetic patients, at least 21 years old, inadequately controlled (HbA1c ≥ 7.5% and ≤ 11%) on insulin with stable doses of mixed, slow acting or intermediary insulins for weeks, + stable dose metformin ≥ 1500 mg/day.

Non-inclusion criteria: treatment with sulphonylureas, glinides, alpha-glucosidase inhibitors or exenatide in the previous 3 months, prior exposure to sitagliptin, use of a rapid-acting, preprandial insulin (>1 injection/day)[7].

Method of administration
641 patients were randomised to be given:
- either the combination of stable dose insulin + sitagliptin 100 mg/d ± metformin (n=322)
- or the combination of stable dose insulin + placebo ± metformin (n=319).

Primary efficacy endpoint:
Mean change in HbA1c at 24 weeks' treatment compared with baseline.

The protocol planned to include 270 patients in both treatment groups to identify a difference of 0.5% ± 1.0% in the change in HbA1c with a power of 99% and statistical threshold of 0.05.

Tests were performed on this endpoint as stipulated in the protocol in the patient subgroups (depending on diabetes treatment at inclusion, baseline HbA1c, BMI, and time since diagnosis of diabetes). No adjustment was made for the multiple comparisons and an overestimation of the effect cannot therefore be excluded. As a result no conclusion can be drawn based on these exploratory tests and they will not be presented.

Main secondary efficacy endpoints after 24 weeks treatment:
- mean change in fasting blood glucose (FBG) and post-prandial glycaemia (PPG)[8]
- glycaemic control in the sub-groups with or without metformin.
- percentage of patients with HbA1c <6.5% and <7%

Tests were ranked[9] and a correction method was used for inflation of statistical results because of the multiple comparisons to avoid overestimating the effect.

6 Insulin mix = mixture of intermediary and rapid acting insulins
[7] Patients using insulin mix (containing a rapid acting insulin) and those who only used occasional rapid acting insulin (≤3 times/week) could be included.
[8] Measured 2 hours after a standard meal of approximately 460 calories containing 75 g of carbohydrates, 9 g of fat and 18 g of protein.
[9] The hypotheses for the secondary endpoints were tested in the following rank order: change in HbA1c in the patient subgroup treated with intermediary/slow acting insulin, change in PPG, change in FBG, proportion of patients who achieved HbA1c < 7.0%, proportion of patients who achieved HbA1c < 6.5%.

Other endpoint:
Mean change in HbA1c at 24 weeks' treatment compared with baseline in the groups of patients who were or were not treated with metformin.[10]

Results:

Results were obtained from the analysis of all patients randomised who did or did not receive at least one dose of the treatment (305/322 patients in the sitagliptin group, 312/319 patients in the placebo group).[11]

Patient characteristics were similar in both treatment groups at inclusion. Patients had:
- average age of 58 years old (22% of patients were 65 years old or older),
- the majority were obese (mean BMI 31.0 kg/m^2).

The diabetes had been present for an average of 12.4 ± 6.6 years.
Mean HbA1c was 8.7± 0.9%. The majority of patients (42%) had an HbA1c of between 8 and 9%. 23.6% of patients had an HbA1c below 8%, and 23.6% of patients had an HbA1c of between 9 and 10%. It should be noted that HbA1c values were high at inclusion.
27.9% of patients were treated with insulin alone and 72.1% received the combination of insulin+metformin. The majority of patients (73.6%) were using intermediary or slow-acting insulin and 26.4% were using an insulin mix. Insulin doses had been stable for more than 6 months in 75% of patients.

The mean daily doses of insulin used were :
- 44.3 U/day (44.2 U/day in the sitagliptin group and 44.5 U/day in the placebo group) for intermediary insulin or slow-acting insulin analogues,
- 70.9 U/day for insulin mix (67.4 U/day for the sitagliptin group and 74.5 U/day for the placebo group).

The average dose of metformin received was 2010 mg in the sitagliptin group and 1969.5 mg in the placebo group.

[10] These patients were not defined as a subgroup in the protocol.
[11] Patients whose dose of insulin was adjusted were not included in this analysis. There were no changes in average daily insulin doses during the study in the sitagliptin group. Mean changes were +1.6 U/d (7.0) in the placebo group because of inadequate glycaemic control.

Table 3: characteristics of the patients included

Age (years)				
Treatment group	N	Mean + SD	Median	Range
Sitagliptin	322	58.3 + 9.1	58.0	25.0 to 80.0
Placebo	319	57.2 + 9.3	58.0	28.0 to 82.0
All	641	57.8 + 9.2	58.0	25.0 to 82.0
Body mass index (kg/m²)				
	N	Mean + SD	Median	Range
Sitagliptin	322	31.4 + 5.4	31.1	20.6 to 43.3
Placebo	319	31.4 + 5.0	30.9	20.3 to 49.3
All	641	31.4 + 5.2	31.1	20.3 to 49.3
HbA1c (%)				
	N	Mean + SD	Median	Range
Sitagliptin	322	8.7 + 0.9	8.6	6.6 to 12.1
Placebo	319	8.6 + 0.9	8.6	6.6 to 11.7
All	641	8.7 + 0.9	8.5	6.6 to 12.1
HbA1c distribution				
	N	Number (%) of patients with HbA1c at inclusion		
		<8%	≥ 8 and < 9%	≥ 9 and <10%	≥ 10%
Sitagliptin	322	68 (21.1)	137 (42.5)	80 (24.8)	37 (11.5)
Placebo	319	83 (26.0)	132 (41.4)	71 (22.3)	33 (10.3)
All	641	151 (23.6)	269 (42.0)	151 (23.6)	70 (10.9)
Fasting blood glucose (mg/dL)				
	N	Mean + SD	Median	Range
Sitagliptin	322	175.6 + 51.8	165.0	63.0 to 376.0
Placebo	319	178.7 + 59.6	170.0	61.0 to 704.0
All	641	177.1 + 55.8	168.0	61.0 to 704.0
Post-prandial glycaemia (mg/dL)				
	N	Mean + SD	Median	Range
Sitagliptin	298	295.2 + 72.3	286.0	112.0 to 587.0
Placebo	301	295.8 + 73.2	289.0	116.0 to 609.0
All	599	295.5 + 72.7	288.0	112.0 to 609.0
Time since diagnosis of type 2 diabetes (years)				
	N	Mean + SD	Median	Range
Sitagliptin	322	12.9 + 7.2	12.0	1.0 to 40.0
Placebo	319	12.0 + 5.9	12.0	0.1 to 36.0
All	641	12.4 + 6.6	12.0	0.01 to 40.0
Treatments for diabetes				
	insulin alone N (%)		insulin + metformin N (%)	Total N
Sitagliptin	93 (28.9)		229 (71.1)	322
Placebo	86 (27.0)		233 (73.0)	319
All	179 (27.9)		462 (72.1)	641
	insulin mix		intermediary or slow-acting insulin	Total
	N (%)		N (%)	N
Sitagliptin	87 (27.0)		235 (73.0)	322
Placebo	82 (25.7)		237 (74.3)	319
All	169 (26.4)		472 (73.6)	641
Treatments for diabetes: use of metformin depending on insulin type				
	insulin mix		Intermediary or slow-acting insulin		Total
	with metformin N (%)	without metformin N (%)	with metformin N (%)	without metformin N (%)	N
Sitagliptin	52 (16.1)	35 (10.9)	177 (55.0)	58 (18.0)	322
Placebo	48 (15.0)	34 (10.7)	185 (58.0)	52 (16.3)	319
All	100 (15.6)	69 (10.8)	362 (56.5)	110 (17.2)	641

Primary efficacy endpoint:

Table 4: change in HbA1c at 24 weeks:

Treatment group	N	Mean initial HbA1c (standard deviation)	Mean adjusted change in HbA1c (SD)	Mean difference/comparator, 95% CI
insulin + sitagliptin ± metformin	305	8.72 (0.88)	-0.65 (0.05)	**- 0.56 [-0.70;-0.42] p<0.001**
insulin + placebo ± metformin	312	8.64 (0.95)	-0.07 (0.05)	

There was a greater fall in HbA1c in patients taking insulin + sitagliptin ± metformin than in those taking insulin + placebo ± metformin after 24 weeks' treatment (difference between sitagliptin and placebo: -0.56%, 95% CI [-0.70; -0.42]; p<0.001).
It should be noted that the effect of sitagliptin was greatest up to the 12th week of treatment. Beyond that, HbA1c levels rose.
In an additional analysis of this endpoint stipulated in the protocol, the difference between sitagliptin and placebo was -0.65% (95% CI [-0.91; -0.39]; p<0.001) in the group of patients who had not received metformin (N=165/617) and -0.53% (95% CI [-0.69; -0.37]; p<0.001) in the group of patients who had received metformin (N=452/617).

Secondary efficacy endpoints:

- mean change in post-prandial glycaemia (PPG):

PPG fell more after 24 weeks' treatment in the sitagliptin + insulin ± metformin group (n-39.0 mg/dl, =240) than in the placebo + insulin ± metformin group (-3.1 mg/dl, n=257): the difference between the treatments was -36.1 mg/dl, 95% CI [-4.7; -25.1], p<0.001.

- mean change in fasting blood glucose (FBG):

FBG fell more after 24 weeks treatment in the sitagliptin + insulin ± metformin group (-20.7 mg/dl, n=310) than in the placebo + insulin ± metformin group (-8.0 mg/dl, n=313), and the difference between the treatments was -15.0 mg/dl, 95% CI [-23.4; -6.5], p<0.001.

- percentage of patients with HbA1c < 7%

The aim of treatment with insulin therapy was achieved in 12.8% of patients analysed in the sitagliptin group (39/305) and 5.1% of patients in the placebo group (16/312).

3.2. Adverse effects

3.2.1. Safety from the monotherapy study (study P049)

At least one adverse event was reported in 198/528 (37.5%) patients in the sitagliptin group and 215/522 (41.2%) patients in the metformin group.
Nine patients (1.7%) in the sitagliptin group reported 17 episodes of hypoglycaemia compared to 17 patients (3.3 %) in the metformin group who reported 23 episodes.

61 patients in the sitagliptin group (11.6%) and 108 patients in the metformin group (20.7%) experienced gastrointestinal adverse events (diarrhoea, nausea, vomiting, abdominal pain).
Weight loss was reported in both treatment groups with a larger fall in the metformin group (-1.9 kg) than in the sitagliptin group (-0.6 kg).

141 patients stopped treatment: 64 in the sitagliptin group and 77 in the metformin group. The main reasons were as follows:

- adverse events in 28 patients (9 on sitagliptin including 3 due to treatment attributable hypoglycaemia, 19 on metformin including 12 due to a treatment attributable event)
- breach of protocol in 29 patients (14 on sitagliptin and 15 on metformin)
- withdrawal of consent by 41 patients (18 on sitagliptin, 23 on metformin).

3.2.2. Safety from the combination study with insulin, plus or minus metformin (study P051)

At least one adverse event was reported in 168/322 patients (52.2%) in the sitagliptin group and 137/319 patients (42.9%) in the placebo group.
The adverse events were treatment-related in 50/322 patients in the sitagliptin group (15.5%) and 27/319 (8.5%) in the placebo group.

The main adverse events reported were:

- infections (influenza, rhinopharyngitis, urinary infections, upper respiratory tract infections) in 20.8% of patients receiving sitagliptin and 17.9% of patients receiving placebo
- hypoglycaemia in 15.5% of patients receiving sitagliptin (i.e. 50 patients who had a total of 155 episodes of hypoglycaemia) and 7.8% of patients receiving placebo (i.e. 25 patients who had a total of 76 episodes). Most hypoglycaemic episodes were mild to moderate in severity.

There were no differences in change in weight between the two treatment groups.
Five cases of a fall in creatinine clearance were reported in the sitagliptin group and described as mild (one case) to moderate (four cases), and only two were deemed to be related to the treatment. These effects will be included in the SPC.[12]

Eleven patients stopped treatment due to an adverse event in the sitagliptin group (including treatment related events in three patients) and four stopped in the placebo group (no treatment-related events).

3.2.3. Post-MA changes in the JANUVIA/JANUMET SPCs on safety (changes dated 26 November 2010 and 24 August 2011)

Since it was first marketed, the SPC has been updated as the following additional adverse effects have been reported (frequency unknown): hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, **cutaneous vasculitis** and exfoliating skin lesions including the Stevens-Johnson syndrome; **pancreatitis,** arthralgia and myalgia.
The information summarised about some of these events by the EMA is shown below:

- Pancreatitis:
  The number of cases reported in the clinical studies is very low. Since sitagliptin was first marketed, 108 cases of (acute) pancreatitis have been reported, 38 of which were inadequately documented. There were confounding variables in two of the fatal cases reported in terms of co-morbidities and concomitant treatments. In light of the available data a causal relationship with the medicine cannot be excluded.
- Cutaneous vasculitis:
  A total of 15 cases have been reported (spontaneous notifications or cases from clinical trials), the majority of which had many confounding variables. Because hypersensitivity reactions are already known effects of sitagliptin and as there was one case of cutaneous vasculitis with a positive re-challenge, the causal relationship is deemed to be likely.

[12] Three of these five cases resulted in patient stopping the study

3.2.4. Update of grouped clinical study data

This analysis involved 19 double-blind, randomised, phase IIb and III studies lasting between 12 weeks and 2 years. Six new published studies have been added since the evaluation performed by the TC in 2009 in the JANUVIA opinion.
The data analysis is limited to those studies in which JANUVIA was administered at a dose of 100 mg/day, consistent with its MA.
The studies chosen included patients treated with sitagliptin monotherapy or with dual therapy from the outset with metformin or pioglitazone, or when one or two other OAD(s) were added (metformin, pioglitazone, sulphonylurea+metformin, insulin+metformin, metformin+rosiglitazone).

"Unexposed" patients in the comparator arms were treated with placebo, OAD monotherapy (metformin, glitazone or sulphonylurea), insulin alone or a combination of OAD (sulphonylurea+metformin, metformin+rosiglitazone) or insulin+metformin.

A total of 10,246 patients were included in this update:
- 5429 in the groups treated with JANUVIA for an average period of 282 days (including 1805 patients treated for ≥ 1 and 584 treated for 2 years),
- 4817 for the control groups which were “unexposed” to JANUVIA, for an average of 259 days (including 1320 patients treated for ≥ 1 year and 470 patients treated for 2 years).

Average patient age was 55 years old (range 19-91). 18% were 65 years old or older. The average time since diagnosis of the diabetes was 3.5 years and the mean baseline HbA1c was 8.4%. 11% of patients in this population were taking secondary cardiovascular prevention at inclusion and 82% had another co-existent cardiovascular risk factor (hypertension in 55%, dyslipidaemia in 50% and smoking in 40% of cases).

The incidence of treatment-related adverse events according to the investigator was significantly higher in the “unexposed” group mostly because of hypoglycaemia due to the sulphonylureas: the between-treatment difference expressed as the number per 100 patient-years was -6.4%, 95% CI [-8.7; -4.1].

No differences were seen between the groups except for:
- metabolic and nutritional disorders: the incidence per 100 patient-years was 9.3% in the sitagliptin group and 16.3% in the “unexposed” group (difference: -6.8%, 95% CI [-8.5; -5.2]). This difference in favour of sitagliptin is mostly explained by a higher incidence of hypoglycaemia in the “unexposed” control group;
- skin and subcutaneous disorders: the incidence per 100 patient-years was 8.6% in the sitagliptin group compared to 7.3% in the “unexposed” group (difference: +1.3%, 95% CI [0.1; 2.5]). This difference was mostly due to a higher incidence of contact dermatitis, macular rash and acne in the sitagliptin group compared to the “unexposed” group.

The incidence of cardiovascular and hepatic events and infection-related events were similar in both treatment groups.

3.2.5. Safety from the last PSUR (covering the period from 4 August 2009 to 3 August 2011)

The analysis of data from the last JANUVIA international PSUR is consistent with the information about the risk as shown in the current MA. Safety is monitored closely in the international RMP.
It should be noted that in addition to the European RMP for JANUVIA/JANUMET, Afssaps has instituted increased national pharmacovigilance monitoring targeted particularly on monitoring for infectious disorders, gastrointestinal disorders, rheumatological disorders and neuropsychiatric disorders.
A total of 7496 adverse event reports were identified, including 1972 reports of serious cases. Twenty-seven of the 7,496 reports were obtained from studies and 7,469 other reports were spontaneous notifications by health professionals.

The cases reported most frequently were:

- gastrointestinal disorders, with a total of 1933 reports, including 2488 events, mostly pancreatitis (459 events), nausea (268) and diarrhoea (244 events)
- skin and subcutaneous tissue disorders with 1,190 events, mostly skin rash (317 events), pruritus (178 events) and urticaria (105 events)
- metabolic and nutritional disorders, with 850 events including hypoglycaemia (628 events), reduced appetite (78 events) and hyperglycaemia (38 events).

There were 1972 reports of serious adverse events during this period which described 3114 serious adverse events occurring on sitagliptin, including 459 cases of pancreatitis, 133 cases of acute pancreatitis, 127 overdoses, 165 cases of hypoglycaemia (90% of hypoglycaemic events occurred in the presence of concomitant treatments (metformin, insulin, sulphonylureas) which are known to increase the risk of hypoglycaemia in patients treated with sitagliptin).

3.3. Conclusion

The evaluation of the efficacy and safety of sitagliptin is based on:

- one double-blind, randomised, phase III study (study P049), the objective of which was to demonstrate non-inferiority of monotherapy with sitagliptin to metformin after 24 weeks of treatment in 1050 type 2 diabetic patients who were inadequately controlled with diet and physical exercise alone and who had not received any previous diabetic treatment for at least 4 months.
  The patient characteristics were similar at inclusion in both treatment groups. Average patient age was 56 years old, most were obese and their mean HbA1c was 7.2 $\pm$ 0.7%.
  The difference in HbA1c reduction between sitagliptin and metformin in the per protocol population after 24 weeks treatment was 0.14%, 95% CI [0.06; 0.21]. The upper limit of the confidence interval of this difference was below the fixed threshold (0.4%) and sitagliptin was therefore demonstrated to be non-inferior to metformin. This result was confirmed in the ITT population.
  The treatment target (HbA1c <6.5%, a secondary efficacy endpoint) was achieved by 33.6% of patients on sitagliptin (153/455) and 39.2% of patients on metformin (172/439). These figures are low.
  This study evaluated patients who were inadequately controlled by diet and physical exercise alone. No data are available in patients in whom metformin was contraindicated or not tolerated.
- one double-blind, randomised, phase III study (study P051), the objective of which was to compare the efficacy and safety of the combination of insulin + sitagliptin ± metformin with that of the combination of insulin + placebo ± metformin, after 24 weeks of treatment in 641 type 2 diabetic patients who were inadequately controlled with insulin using mixed, slow-acting or intermediary-acting insulins at stable doses for 10 weeks.
  The patient characteristics were similar at inclusion in both treatment groups. On average, the patients were 58 years old, and obese. The majority had an HbA1c of between 8 and 9% and 72.1% of patients were taking a combination of insulin+metformin.
  The fall in HbA1c (primary efficacy endpoint) was greater in patients on insulin + sitagliptin ± metformin than in those on insulin + placebo ± metformin after 24 weeks treatment (difference between sitagliptin and placebo: -0.56%, 95% CI [-0.70; -0.42]; p<0.001). This fall was in the same order of magnitude in the groups of patients who were or were not taking metformin.
  The aim of treatment with insulin therapy was achieved in 12.8% of patients analysed in the sitagliptin group (39/305) and 5.1% of patients in the placebo group (16/312). The patient response rate was low.

It should be noted that the effect of sitagliptin was greatest up to 12 weeks of treatment in each of the studies. This is a modest effect in terms of the fall in HbA1c compared to existing alternatives[13] but is of the same order of magnitude as is seen with the other gliptins.[14, 15, 16]

The main adverse events were hypoglycaemia and gastrointestinal disorders in the monotherapy study and infections and hypoglycaemia in the insulin combination study.
The SPC has been updated since the proprietary medicinal products containing sitagliptin were first marketed as the following additional adverse effects have been reported (unknown frequency): hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis and exfoliating skin lesions including the Stevens-Johnson syndrome; pancreatitis, arthralgia and myalgia.

No studies have shown sitagliptin to be superior in its MA indications compared to a reference treatment.[17]
There are no morbidity and mortality data, although one study is ongoing.

[13] Mean changes in HbA1c found were in the region of:
- -1 to -1.5% with metformin
- -1 to -1.5% with the sulphonylureas
- -0.8% with the glinides
- -0.5 to 1% with the alpha-glucosidases.

[14] 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.
[15] Richter B. et al. Dipeptidyl peptidase-4 inhibitors for type 2 diabetes mellitus. The Cochrane Database of Systematic Reviews 2008, Issue 2
[16] Don Dicker et al. DPP-4 inhibitors. Impact on glycemic control and cardiovascular risk factors. Diabetes Care, Vol 34, Supplement 2, May 2011.
[17] T. Karagiannis and al. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. BMJ. 2012 March 12; 344: e1369. doi: 10.1136/bmj.e1369.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

4.1.1. As monotherapy

Type 2 diabetes is a chronic disease with potentially serious, particularly cardiovascular, complications.
JANUVIA is used for the treatment of hyperglycaemia.

The efficacy of JANUVIA in its monotherapy indication has only been demonstrated in a non-inferiority study against metformin. A superiority study against active comparators such as metformin or sulphonylureas would have enabled the benefit of the proprietary medicinal product as monotherapy to be evaluated, particularly in light of the large fall which is seen with these comparators (in the region of -1 to -1.5%), which have also been shown to have a strongly positive impact on morbidity and mortality.[18] In addition, the proportion of patients who responded (HbA1c < 6.5%) to JANUVIA monotherapy is low (33.6% of patients on sitagliptin compared to 39.2% of patients on metformin).
This study evaluated patients who were inadequately controlled by diet and physical exercise alone. No data are available in patients in whom metformin was contraindicated or not tolerated.
For these reasons, the efficacy/adverse effects ratio of JANUVIA monotherapy cannot be described.

In light of the data available, this proprietary medicinal product cannot be recommended as monotherapy. Alternative medicines to this proprietary medicinal product exist for the treatment of diabetic patients (principally metformin and sulphonylureas). If metformin is contraindicated, the main medicines recommended are sulphonylureas and insulin in moderate renal impairment and insulin in severe renal impairment. Dual therapy may be considered if correct monotherapy with treatments which have been proven to be effective fails.

Public health benefit:
The burden of type 2 diabetes is substantial because of its high and constantly increasing prevalence and its microvascular and macrovascular complications. The burden in the subpopulation of patients for whom JANUVIA monotherapy is indicated is deemed to be moderate.
Improvement in the therapeutic management of type 2 diabetic patients is a public health need included in the established public health priorities.[19]
In light of the results of the non-inferiority clinical study against metformin in this indication, JANUVIA is not expected to have an impact on the glycaemic control of patients who are treated with it. It would not therefore be expected to have an impact on morbidity and mortality or quality of life of treated patients.
In addition, it is not clear whether the experimental data can be extrapolated to 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 JANUVIA does not provide a response to the identified public health need.
Consequently, it is not expected that the proprietary medicinal product JANUVIA will benefit public health in this indication.

[18] 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.
19 Objective 55 of the Law of 9 August 2004 relating to Public Health Policy: Reducing the frequency and severity of diabetes complications and particularly cardiovascular complications, national plan to improve quality of life in people suffering from chronic diseases 2007-2011.

The transparency Committee therefore considers that the actual benefit of the proprietary medicinal product JANUVIA is insufficient for reimbursement by National Health Insurance as monotherapy in patients who are inadequately controlled by diet and physical exercise alone and in whom metformin is contraindicated or not tolerated.

4.1.2. As dual in combination with insulin

Type 2 diabetes is a chronic disease with potentially serious, particularly cardiovascular, complications.
JANUVIA is used for the treatment of hyperglycaemia.

Only 27.9% of patients were being treated at inclusion with insulin alone in the placebo-controlled study in combination with insulin. Dual therapy with insulin + sitagliptin was therefore evaluated in a very small number of patients.

A study comparing the combination of insulin + sitagliptin with insulin + metformin or with insulin + sulphonylurea would have been able to quantify the utility and benefit of this dual therapy for which no recommendation is made. The only antidiabetic agents recommended in combination with insulin and used in practice are metformin and the sulphonylureas.
For this reason the efficacy/adverse effects ratio of JANUVIA in dual therapy added to insulin cannot be described.

In light of the available data this proprietary medicinal product cannot be recommended in combination with insulin as dual therapy. The reference treatment to add when insulin treatment is started is metformin. In a systematic review[20] which included 23 trials and a total of 2117 patients, and evaluated metformin combined with insulin compared with insulin alone, the insulin + metformin combination was associated with a larger fall in HbA1c (between-group difference -0.60%, 95% CI [-0.89; -0.31] p<0.001) and with weight gain (+ 1 kg) compared with insulin alone. According to the guidelines,[21, 22] the validated combinations when insulin therapy is started to maintain or improve glycaemic control as dual therapies are insulin + metformin or insulin + sulphonylurea.

Public health benefit:

The burden of type 2 diabetes is substantial because of its high and constantly increasing prevalence and its microvascular and macrovascular complications. The burden in the subpopulation of patients for whom JANUVIA monotherapy is indicated is deemed to be moderate.
Improvement in the therapeutic management of type 2 diabetic patients is a public health need included in the established public health.[23]
In light of the results of the placebo-controlled clinical study in this indication, the proprietary medicinal product JANUVIA is not expected to have impact on glycaemic control. It would not therefore be expected to have an impact on morbidity and mortality or quality of life in patients treated over the currently available dual therapies.
In addition, it is not clear whether the experimental data can be extrapolated to 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, no presumptions may be made as to the response provided by JANUVIA to the identified public health need.
Consequently, it is not expected that the proprietary medicinal product JANUVIA will benefit public health.

[20] 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.
[21] Scottish Intercollegiate Guidelines Network SIGN; 2010, Management of diabetes. A national clinical guideline. March 2010. http://www.sign.ac.uk/pdf/sign116.pdf
[22] 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.
23 Objective 55 of the Law of 9 August 2004 relating to Public Health Policy: Reducing the frequency and severity of diabetes complications and particularly cardiovascular complications, national plan to improve quality of life in people suffering from chronic diseases 2007-2011.

The transparency Committee therefore considers that the actual benefit of the proprietary medicinal product JANUVIA is insufficient for reimbursement by National Health Insurance in light of the alternatives which exist, as dual therapy in addition to insulin when a stable dose of insulin together with diet and physical exercise do not achieve adequate glycaemic control.

4.1.3. As triple therapy in combination with insulin and metformin

Type 2 diabetes is a chronic disease with potentially serious, particularly cardiovascular, complications.
JANUVIA and JANUMET are used for the treatment of hyperglycaemia.

The efficacy/adverse effects ratio for these proprietary medicinal products is high. However the long-term risks, particularly in terms of pancreatic and cutaneous adverse events, are poorly understood.

They are treatments to be used as triple therapy in combination with insulin and metformin.
There are alternative medicines to these proprietary medicinal products.

Public health benefit:

The burden of type 2 diabetes is substantial because of its high and constantly increasing prevalence and its microvascular and macrovascular complications. The burden in the subpopulation of patients for whom JANUVIA and JANUMET is indicated as triple therapy is deemed to be moderate.

Improvement in the therapeutic management of type 2 diabetic patients is a public health need included in the established public health priorities.[24]

In light of the results of the placebo-controlled clinical study in this indication, the proprietary medicinal products JANUVIA and JANUMET are not expected to have impact on glycaemic control. They would not therefore be expected to have an impact on morbidity and mortality or quality of life in patients treated over the currently available triple therapies.

In addition, it is not clear whether the experimental data can be extrapolated to 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, no presumptions may be made as to the response provided by JANUVIA and JANUMET to the identified public health need.

Consequently, it is not expected that the proprietary medicinal products JANUVIA and JANUMET will benefit public health.

The actual benefit of JANUVIA and JANUMET is substantial in triple therapy in combination with insulin and metformin.

24 Objective 55 of the Law of 9 August 2004 relating to Public health Policy: Reducing the frequency and severity of diabetes complications and particularly cardiovascular complications, national plan to improve quality of life in people suffering from chronic diseases 2007-2011.

4.2. Improvement in actual benefit (IAB)

- In the monotherapy and dual therapy indications in combination with insulin: not applicable

- In the triple therapy indication :

As triple therapy, in combination with stable doses of insulin and metformin in patients who have not achieved adequate glycaemic control, JANUVIA and JANUMET do not provide an improvement in actual benefit (IAB V) in the management of these type 2 diabetic patients.

4.3. Therapeutic use

The objectives of therapeutic management are glycaemic control: control of HbA1c and control of co-existing risk factors.

The choice of medical treatment and treatment targets must be adapted for individual patients (age, time since diagnosis of the diabetes, specific situations risk of hypoglycaemia, etc.).

Type 2 diabetic patients are treated initially with lifestyle and dietetic measures which must be continued at all stages.

Antidiabetic agents are used when lifestyle and dietetic measures are no longer sufficient to control blood sugar.
Combating sedentary lifestyle and dietary planning are essential interventions at all stages in the management of this disease.

If, despite maximum dose monotherapy, the patient's HbA1c is > 6.5%, the following dual therapies are then used:
- metformin + insulin secretagogue
- metformin + alpha-glucosidase inhibitor
- or insulin-secretagogue + alpha-glucosidase inhibitor (where there is significant post-prandial hyperglycaemia but it is less effective on HbA1c than the other combinations).

If the patient's HbA1c is > 7%, triple therapy or insulin combined with metformin or other oral antidiabetic agents excluding glitazones is used.
This treatment strategy is currently being revised by HAS. The place of GLP-1 analogues and DPP-4 inhibitors remains to be established.

The last updates of the international guidelines describe strategies following on from the results of the major trials (VADT, ACCORD, ADVANCE and the 10 year follow-up UKPDS results) and the availability of the incretin mimetic medicines.
In particular, the NICE guidelines[25] position the existing DPP-4 inhibitors in dual therapy in combination with oral antidiabetic agents or in triple therapy. They also suggest that treatment with new medicines may only be continued if a significant fall in HbA1c is achieved at 6 months: -0.5% for the DPP-4 inhibitors, -1% for exenatide (a GLP-1 analogue).

The last ADA/EASD guidelines[26, 27] also propose changing the target HbA1c (7% to reduce microvascular risk). These guidelines also propose a management algorithm based on rapid

[25] 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

[26] 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.

escalation of management using medicines which have already been proven on clinical criteria (metformin and insulin).

The SIGN guidelines (Scottish Intercollegiate Guidelines Network),[28] state that HbA1c targets should be adapted according to the patient's profile,[29] and give an estimate of the quantitative effects of the DPP-4 inhibitors[30] or gliptins, positioning the DPP-4 inhibitors in dual therapy as an alternative to sulphonylureas in patients in whom hypoglycaemia or weight gain may pose a problem, and recognize as a third line treatment the move from one dual therapy to another dual therapy as an alternative to direct escalation.

Place of JANUVIA/JANUMET in therapeutic strategy

Dual therapy from the outset or insulin therapy may be offered as first-line treatment to patients with a high HbA1c (>9.0%).

Some patients do not achieve or maintain glycaemic targets on insulin therapy alone. It is then recommended that insulin be combined with another antidiabetic agent. In practice it is metformin which is widely used in combination with insulin.[31]

If metformin is contraindicated or not tolerated, sulphonylureas are offered. If targets are not achieved with these dual therapies, the doses of insulin can be increased although this dose escalation is often associated with increased risk of hypoglycaemia and weight gain. Sitagliptin therefore is a treatment option which can be added to the insulin + metformin combination.

It should be noted that JANUVIA has no role in the treatment strategy for type 2 diabetic patients, either as monotherapy or as dual therapy in combination with insulin.

4.4. Target population

According to the actual benefit defined by the Committee, the target population for JANUVIA and JANUMET is type 2 diabetic patients who are treated:

- in addition to insulin with metformin when a stable dose of insulin, together with diet and physical exercise, do not achieve adequate glycaemic control.

As a reminder, the prevalence of pharmacologically treated diabetes in France was estimated by the French National Health Insurance to be 4.4% in 2009,[32] i.e. 2.9 million people. The annual growth rate is estimated to be 4.7% (calculated from the general system data).

In light of the 2009 prevalence and its increase, the prevalence of treated diabetes was believed to be almost 3.03 million people in 2010.

The ENTRED study 2007-2010 data also provide further information.[33,34,35]

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[27] 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.

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

[29] A target HbA1c value of 7.0% is a reasonable goal to reduce the risk of microvascular and macrovascular disease. A target of 6.5% may be relevant at the time of diagnosis.

[30] Compared to placebo, sitagliptin, vildagliptin and saxagliptin reduce HbA1c by 0.7%, 0.6% and 0.6% respectively.

[31] 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.

[32] 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. What have been the changes between 2000 and 2009 in France?] *BEH 2010; 42-43: 425-31.*

[33] Representative national reference sample of diabetic people (Entred) 2007-2010 Slide set: Characteristics of diabetic people, vascular risk, complications of medical management (update of 12 March 2010).
http://www.invs.sante.fr/surveillance/diabete/entred_2007_2010/resultats_metropole_principaux.htm

[34] Fagot-Campagna A, Fosse S, Roudier C, Romon I, Penfornis A, Lecomte P, Bourdel-Marchasson I, Chantry M, Deligne J, Fournier C, Poutignat N, Weill A, Paumier A, Eschwège E, for the Entred Scientific Committee. Caractéristiques, risque vasculaire et complications chez les personnes diabétiques en France métropolitaine : d'importantes évolutions entre Entred 2001 et Entred 2007. [Characteristics, vascular risk and complications in diabetic people in mainland France: important developments between Entrad 2001 and ENtrad 2007] *BEH. 2009: 42-43: 450-455.*

[35] Fagot-Campagna A, Romon I et al. (French Health Monitoring Institute) Prevalence of incidence of diabetes and mortality from diabetes in France *http://www.invs.sante.fr/publications/2010/plaquette_diabete/plaquette_diabete.pdf*

91.9% of diabetic patients are believed to be type 2 diabetics, i.e. approximately 2.79 million people.

➢ Population in the indication for use in combination with insulin + metformin :

Populations considered	Numbers considered	Comments	Sources
Patients treated with insulin in 2007 (23% of T2DM patients in 2007)	358,000		LANTUS TC opinion (2009)
- Of which insulin alone (39.0%) **- Of which insulin + OAD (61.0%)**	139,620 218,380	14.1% of patients with T2DM are treated with insulin, including 5.5% with insulin alone.	ECODIA 2 Study, March 2007
Sub-population on insulin + OAD - 51.5% with HbA1c >7%	218,380 112,465		ECODIA 2 Study, March 2007
Total target population in this indication	**112,465 patients**		

The target population for JANUVIA and JANUMET in the extension to indication of use in combination with insulin and metformin as triple therapy would be in the region of 113,000 patients.

4.5. Transparency Committee recommendations

➢ In the indications for use as monotherapy and dual therapy in combination with insulin:

The transparency Committee does not recommend inclusion of the proprietary medicinal product JANUVIA on the list of medicines refundable by National Health Insurance and on the list of medicines approved for use by hospitals and various public services.

➢ In the indication for use as triple therapy in combination with insulin and metformin:

The transparency Committee recommends inclusion of the proprietary medicinal products JANUVIA and JANUMET on the list of medicines refundable by National Health Insurance (B/28 for JANUVIA, B/56 for JANUMET) and on the list of medicines approved for use by hospitals and various public services (B/28 and B/50 for JANUVIA, B/56 and B/50 for JANUMET) in the above indication at the dosage in the Marketing Authorisation.

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

The transparency Committee would like the follow-up study requested in 2007 to be extended to the patients affected by these extensions of indications.