



HAUTE AUTORITÉ DE SANTÉ

**The legally binding text is the original French version**

**TRANSPARENCY COMMITTEE**

Opinion

6 June 2007

**JANUVIA 100 mg, film-coated tablets**

**B/28 (CIP: 379,250-4)**

**B/50 (CIP: 570,745-4)**

**Applicant: MERCK SHARP & DOHME-CHIBRET**

Sitagliptin

List 1

ATC Code: A10BH01

Date of Marketing Authorisation: March 21, 2007

Reason for request:

Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals : box of 28

Inclusion on the list of medicines approved for use by hospitals: box of 50

Health Technology Assessment Division

# 1. PROPERTIES OF THE MEDICINAL PRODUCT

## 1.1. Active substance

Sitagliptin

## 1.2. Background

Sitagliptin is an oral hypoglycaemic agent belonging to a new class, namely dipeptidylpeptidase-4 (DPP-4) inhibitors. The improvement in blood glucose control observed with sitagliptin may be explained by the increased level of active incretin hormones.

## 1.3. Indications

*For patients with type 2 diabetes mellitus, Januvia is indicated:*

- to improve glycaemic control in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- to improve glycaemic control in combination 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.
- to improve glycaemic control in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.

*For patients with type 2 diabetes mellitus in whom use of a PPAR $\gamma$  agonist (i.e. a thiazolidinedione) is appropriate, Januvia is indicated:*

- in combination with the PPAR $\gamma$  agonist when diet and exercise plus the PPAR $\gamma$  agonist alone do not provide adequate glycaemic control.

## 1.4. Dosage (see SPC)

The dose of Januvia is 100 mg once daily. The dosage of metformin or PPAR $\gamma$  agonist should be maintained, and sitagliptin administered concomitantly.

When Januvia is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia (See section 4.4. of 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 can be taken with or without food.

### Patients with renal insufficiency

For patients with mild renal insufficiency (creatinine clearance [CrCl]  $\geq$  50 ml/min), no dosage adjustment for Januvia is required.

Clinical study experience with Januvia in patients with moderate or severe renal insufficiency is limited. Therefore, use of Januvia is not recommended in this patient population (see section 5.2).

Patients with hepatic insufficiency

No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency. Januvia has not been studied in patients with severe hepatic insufficiency.

Elderly

No dosage adjustment is necessary based on age. Limited safety data is available in patients  $\geq 75$  years of age and care should be exercised.

Paediatric population

Januvia is not recommended for use in children under 18 years of age due to a lack of data on its safety and efficacy.

**1.5. Special warnings and precautions for use (see SPC)**

As experience is limited, patients with moderate to severe kidney failure must not be treated with Januvia.

## 2. SIMILAR MEDICINAL PRODUCTS

### 2.1. ATC Classification

<b>A</b>	Gastrointestinal tract and metabolism
<b>A10</b>	Drugs used in diabetes
<b>A10B</b>	Antidiabetics, apart from insulin
<b>A10BH</b>	Other antidiabetics, apart from insulin
<b>A10BH01</b>	Dipeptidylpeptidase-4 (DPP-4) inhibitors

### 2.2. Medicines in the same therapeutic category

None.

### 2.3. Medicines with a similar therapeutic aim

The medicines with a similar therapeutic aim are antidiabetics, which can be added to metformin or glitazone for the purpose of antidiabetic bitherapy:

- Indicated in type 2 diabetics who have not achieved adequate blood glucose control at the maximum tolerated doses of an oral treatment based on metformin in monotherapy:

- hypoglycaemic sulphonylureas
- glitazones
- intestinal alpha-glucosidase inhibitor (acarbose)
- glinide
- incretin mimetic;

- Indicated in type 2 diabetics who have not achieved adequate blood glucose control at the maximum tolerated doses of an oral treatment based on glitazone in monotherapy:

- none.

## 3. ANALYSIS OF AVAILABLE DATA

The efficacy and safety data analysis is based on 3 clinical trials submitted by the manufacturer:

- Two placebo-controlled trials of sitagliptin,
  - **trial 020**, conducted in combination with metformin<sup>1</sup> in patients poorly controlled with metformin alone.
  - **trial 019**, conducted in combination with pioglitazone<sup>2</sup> in patients poorly controlled with pioglitazone alone.
- A sitagliptin trial vs. glipizide<sup>3</sup>,
  - **trial 024**, conducted in combination with metformin in patients poorly controlled with metformin alone.

The safety analysis in patients exposed to sitagliptin was completed by the results of phase II trials (P010 and P014) and phase III trials, off-label, in monotherapy (P021, P023, P036) or bitherapy (P035, sulphonylurea + sitagliptin versus sulphonylurea, the efficacy results for which are unavailable).

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1 Biguanide class

2 Glitazone class

3 Sulphonylurea class

### 3.1. Efficacy vs. placebo: trials 020<sup>4</sup> and 019<sup>5</sup>

These two comparative, randomised, double-blind trials had the primary objective of evaluating the efficacy and safety of sitagliptin in combination with metformin or pioglitazone compared with a placebo, in patients suffering from type 2 diabetes poorly controlled (HbA1c level  $\geq 7\%$  and  $\leq 10\%$ ) with metformin monotherapy (trial 020) or pioglitazone<sup>6</sup> (trial 019).

#### Design

During the selection period, the patients were either untreated or treated with hypoglycaemic monotherapy or a combination based on metformin (trial 020) or glitazone (trial 019).

Next, in trial 020, the patients received, during a pre-inclusion period, metformin alone at a stable dose  $\geq 1500$  mg/day, first on an open-label basis (up to 10 weeks), and then single-blinded (2 weeks).

In trial 019 the patients received, during a pre-inclusion period, pioglitazone alone at the dose of 30 mg/day or 45 mg/day on an open-label basis (up to 14 weeks), and then single-blinded (2 weeks).

Patients suffering from moderate to severe kidney failure were excluded from these trials.

#### Treatments used in trial 020:

Seven hundred and one patients (N=701), aged 19 to 79 years, were randomised in a 2/1 ratio to receive for 24 weeks one of the two treatments:

- Sitagliptin 100 mg/day, once a day before breakfast, and metformin  $\geq 1500$  mg/day (N = 464),
- Placebo and metformin  $\geq 1500$  mg/day (N=237).

An 80-week open-label extension stage was also conducted<sup>7</sup>. The patients received either sitagliptin 100 mg/day and metformin, or glipizide 5 mg/day and metformin. This extension stage is not described in detail in the present opinion.

#### Treatments used in trial 019:

Three hundred and fifty-three patients (N=353), aged 24 to 87 years, were randomised to receive for 24 weeks one of the two treatments:

- Sitagliptin 100 mg/day, once a day before breakfast, and pioglitazone 30 mg/day or 45 mg/day (2 or 3 tablets) (N=175),
- Pioglitazone 30 mg/day or 45 mg/day and a placebo (N=178).

#### Inclusion criteria:

Type 2 diabetics, aged over 18 years, with an HbA1c level  $\geq 7\%$  and  $\leq 10\%$ ,

- Trial 020: poorly controlled by treatment with metformin ( $\geq 1500$  mg/day) in monotherapy.
- Trial 019: poorly controlled by treatment with pioglitazone (30 or 45 mg/day) in monotherapy.

#### Primary efficacy endpoint:

- Mean change in the HbA1c rate after 24 weeks' treatment vs. placebo.

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4 Charbonnel B et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. Diabetes Care. 2006 Dec;29(12):2638-2643 et rapport d'étude

5 Rosenstock J et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther 2006;28:1556-1568 and study report

6 proprietary drugs based on pioglitazone: ACTOS 15, 30, 45 mg;

7 from which patients who had not attained the objective of blood glucose control after 24 weeks, and had received rescue medication with pioglitazone, were excluded

Secondary endpoints taken into account in this opinion:

- Clinical course of the fasting blood glucose level, estimated after 24 weeks' treatment compared with baseline value,
- Percentage of patients with HbA1c < 6.5% evaluated after 24 weeks' treatment.

Other secondary endpoints not illustrated in detail in this opinion:

- Proinsulin and fasting insulin, proinsulin/insulin ratio, HOMA-β, HOMA-IR<sup>8</sup> QUICKI<sup>9</sup>, percentages of patients with an HbA1c level < 7%, < 7.5%, modification of lipid parameters, percentage of patients requiring rescue medication<sup>10</sup> and lead time, blood glucose profile after standard meal test, parameters measured 2 hours after the meal: insulin, C-peptide, area under curve (AUC) parameters starting from test meal at 3 points, indices of beta cell function and insulin sensitivity starting from test meal at 9 points.

Results

The results of these studies are based on analysis of all patients, ie. those who were randomised and received at least one dose of the treatment (tables 1 and 2). The mean baseline HbA1c level was 8%. Moreover, 55% (trial 020) and 53% of patients (trial 019) had a baseline level < 8%, while 14.3% (trial 020), and 16.5% (trial 019) had a baseline level ≥ 9%.

**Table 1 - Trial 020: combination with metformin**

	metformin combined with	
	sitagliptin 100 mg	placebo
N (randomised)	464	237
N (all patients treated)	453 (97.6%)	224 (94.5%)
Average age (years)*	54.5 ± 10.2 (extreme values 19 to 78)	
Mean baseline BMI (kg/m2) *	31.1 ± 5.2 (extreme values 19.6 to 43.9)	
<b>Variation in HbA1c (%)</b>		
mean baseline HbA1c (SD)	7.96 (0.81)	8.03 (0.82)
<b>Variation compared with initial state, LS-mean</b>	<b>-0.67</b>	<b>-0.02</b>
95% CI	(-0.77,-0.57)	(-0.15,0.10)
<b>Difference between groups, LS-mean</b>	<b>-0.65</b>	
95% CI	<b>(-0.77,-0.53)</b>	
	<b>p* &lt;0.001</b>	
<b>Variation in fasting blood glucose level (g/l)</b>		
Baseline fasting blood glucose level (SD)	1.70 (0.411)	1.735 (0.416)
<b>Variation compared with initial state, LS-mean</b>	<b>-0.169</b>	<b>+0.085</b>
95% CI	(-0.215,-0.123)	(0.029, 0.141)
<b>Difference between groups, LS-mean</b>	<b>-0.254</b>	
95% CI	<b>(-0.310,-0.198)</b>	
	<b>p* &lt;0.001</b>	
<b>% of patients with an HbA1c rate &lt; 6.5% after 24 weeks</b>	<b>17.2%</b>	<b>4.9%</b>
	(n = 78/453)	(n = 11/224)
Difference between treatments, 95% CI	12.3% (7.4,17.2)	
Odds ratio, 95% CI	4.5 (2.25,8.98) p** <0.001	

LS: least square \* all treated patients p \*according to ANCOVA model p \*\*according to logistical regression model

8 evaluation of insulin resistance according to the homeostasis model  
9 quantitative insulin sensitivity check index  
10 with pioglitazone (trial 020) or metformin (trial 019)

**Table 2 - Trial 019: combination with pioglitazone**

	pioglitazone combined with	
	sitagliptin 100 mg	placebo
N (randomised)	175	178
N (all treated patients)	163 (93.1%)	174 (97.8%)
Mean age (years)*	56.9 ± 8.9 (extreme values 24 to 87)	
mean baseline BMI (kg/m2)*	31.5 ± 5.1 (extreme values 20.1 to 44.2)	
<b>Variation in HbA1c (%)</b>		
mean baseline HbA1c level (SD)	8.05 (0.81)	8.00 (0.83)
Variation compared with baseline LS-mean 95% CI	-0.85 (-0.98,-0.72)	-0.15 (-0.28,-0.03)
<b>Difference between groups, LS-mean 95% CI</b>	<b>-0.70 (-0.85,-0.54) p* &lt;0.001</b>	
<b>Mean variation in fasting blood glucose level (g/l)</b>		
Baseline fasting blood glucose level (SD)	1.683 (0.395)	1.656 (0.399)
<b>Variation compared with initial state, LS-mean 95% CI</b>	<b>-0.167</b> (-0.224,-0.110)	<b>0.010</b> (-0.043, 0.063)
<b>Difference between groups, LS-mean 95% CI</b>	<b>-0.177 (-0.243,-0.110) p* &lt;0.001</b>	
<b>% of patients with an HbA1c level &lt; 6.5% after 24 weeks</b>	<b>23.9%</b> (n = 39/163)	<b>4.6%</b> (n = 8/174)
<b>Difference between treatments 95% CI Odds ratio, 95% CI</b>	19.3% (12.1 ; 26.6) 8.95 (3.79,21.10), p** <0.001	

LS: least square \* all treated patients p\*according to ANCOVA model p\*\* according to logistical regression model

For the primary endpoint:

After 24 weeks' treatment, the reduction in HbA1c level was greater:

- In trial 020, in the group of patients treated with metformin+sitagliptin than in the group treated with metformin alone: -0.67% vs. -0.02% (difference between treatments: -0.65%, 95% CI [-0.77,-0.53]; p<0.001).
- In trial 019, in the group of patients treated with pioglitazone+sitagliptin than in the group treated with pioglitazone alone: -0.85% vs. -0.15% (difference between treatments: -0.70%, 95% CI [-0.85,-0.54]; p<0.001).

For the secondary endpoints:

Fasting blood glucose level:

The reduction in fasting blood glucose level was greater:

- In trial 020, in the group treated with metformin+sitagliptin than in the group treated with metformin alone: -0.169 g/l vs +0.085 g/l (difference between treatments: -0.254, 95% CI [-0.310,-0.198]; p <0.001)
- In trial 019, in the group treated with pioglitazone+sitagliptin than in the group treated with pioglitazone alone: - 0.167 g/l vs. + 0.010 g/l (difference between treatments: -0,177, 95% CI [-0.243,-0.110]; p <0.001).

Percentage of patients who reached an HbA1c level of < 6.5%:

The percentage of patients who reached an HbA1c level of < 6.5% was greater:

- In trial 020, in the group treated with metformin +sitagliptin than in the group treated with metformin alone (17.2% versus 4.9%; OR =4.5, 95% CI [2.25,8.98], p<0.001)
- In trial 019, in the group treated with pioglitazone + sitagliptin than in the group treated with pioglitazone alone (23.9% vs. 4.6%; OR =8.95, 95% CI [3.79, 21.10], p<0.001)

### **3.2 Efficacy vs. active comparator: glipizide<sup>11</sup>, sulphonylurea**

#### **Trial 024<sup>12</sup>**

The main purpose of this randomised double-blind trial was to demonstrate that the combination metformin+sitagliptin is not inferior to the combination metformin+sulphonylurea in reducing HbA1c levels in patients suffering from poorly controlled type 2 diabetes (HbA1c level  $\geq 6.5\%$  and  $\leq 10\%$ ) with metformin monotherapy.

#### **Design:**

During the selection period, the type 2 diabetics were either untreated, or treated with a hypoglycaemic agent in monotherapy or oral bitherapy based on metformin. A preinclusion period (up to 19 weeks) included diet and physical exercise and treatment with metformin alone at the dose  $\geq 1500$  mg/day on an open-label basis (up to 16 weeks) and then single-blinded (2 weeks).

Patients suffering from moderate to severe kidney failure were excluded from this trial.

#### **Treatments:**

One thousand one hundred and seventy-two patients (N=1172) aged 24 to 79 years were randomised to receive for 52 weeks one of the two treatments:

- Sitagliptin 100 mg/day, 1 tablet/day before breakfast, combined with metformin  $\geq 1500$  mg/day (N= 588),
- Glipizide<sup>13</sup>, 5 mg/day and up to 20 mg/day, 1 tablet/day before breakfast for the starting dose or twice a day before breakfast and dinner for the other doses (10, 15, 20 mg/day, combined with metformin  $\geq 1500$  mg/day (N=584).

#### **Inclusion criteria:**

Type 2 diabetics aged 18 at 78 years, with an HbA1c level  $\geq 6.5\%$  and  $\leq 10\%$  in metformin monotherapy at a stable dose  $\geq 1500$  mg/day.

#### **Primary efficacy endpoint:**

Mean variation in HbA1c level after 52 weeks' treatment compared with baseline value; hypothesis of non-inferiority of the combination sitagliptin/metformin to glipizide/metformin in terms of reduction in HbA1c level; upper limit of the bilateral 95% confidence interval of the mean difference in HbA1c between sitagliptin/metformin and glipizide/metformin below the predefined non-inferiority margin:  $\delta = 0.3\%$ .

#### **Secondary endpoints taken into account in this opinion:**

- Variation in fasting blood glucose level after 52 weeks' treatment compared with the baseline value.
- Percentage of patients with HbA1c  $< 6.5\%$  after 52 weeks' treatment.

**Other criteria not illustrated in the opinion:** proinsulin and fasting insulin, proinsulin/insulin ratio, HOMA- $\beta$ , HOMA-IR<sup>14</sup>, QUICKI<sup>15</sup>, percentage of patients with HbA1c  $< 7\%$ , modification of lipid parameters, appetite questionnaire.

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11 glipizide-based medicinal products: GLIBENESE, MINIDIAB, OZIDIA SLOW RELEASE (PFIZER), GLIPIZIDE MERCK 5 mg  
12 Nauck MA et al, efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulphonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab. 2007 Mar;9(2):194-205 et rapport d'étude

13 The dose of glipizide administered daily could be increased on each check-up until Consultation 9/Week 18. The maximum dose was 20 mg/day. Dose increase should be based on measurement of capillary blood glucose and clinical evaluation.

14 evaluation of insulin resistance according to the homeostasis model

15 quantitative insulin sensitivity check index



## Results

The results set out in table 3 below are based on the per-protocol analysis. Two hundreds and two patients (34%) in the sitagliptin group (N=588) and 172 patients (29%) in the glipizide group (N=584) discontinued the treatment due to inefficacy (15% in the sitagliptin group and 10% in the glipizide group) or adverse clinical or biological events (4% in each group) or for other reasons (15% in each group).

The mean dose of glipizide used in the comparator group was 10 mg/day, with approx. 40% of patients requiring a dose of glipizide  $\leq$  5 mg/day throughout the trial. However, discontinuance of the treatment due to inefficacy was more frequent in the sitagliptin group than the glipizide group.

The mean baseline HbA1c level was approx. 7.5%; 75% of patients (per-protocol population) had baseline HbA1c levels  $<$  8% and 10% of the values  $>$  9%.

**Table 3 - Trial 024: metformin/sitagliptin vs. metformin/glipizide**

	Metformin combined with	
	sitagliptin 100 mg	glipizide
N (randomised)	588	584
N (per-protocol)	382 (65,0%)	411 (70,4%)
Mean age (years)*	56.9 $\pm$ 8.9 (extreme values 23 to 79)	
Mean baseline BMI (kg/m <sup>2</sup> )*	31.2 $\pm$ 4.9 (extreme values 19.3 to 43.7)	
<b>Variation in HbA1c (%) compared with initial state</b>	N=382	N=411
Mean baseline HbA1c level (SD)	7.48 (0.76)	7.52 (0.85)
<b>Variation compared with initial state, LS-mean (95% CI)</b>	<b>-0.67</b> (-0.75,-0.59)	<b>-0.67</b> (-0.75,-0.59)
<b>Difference between treatments, LS-mean (95% CI)</b>	<b>-0.01</b> (-0.09,0.08)	
<b>Mean variation in fasting blood glucose level (g/l)</b>	N=382	N=407
Mean baseline blood glucose level (SD)	1.575 (0.337)	1.591 (0.386)
<b>Variation compared with initial state, LS-mean (95% CI)</b>	<b>-0.100</b> (-0.146 ; -0.054)	<b>-0.075</b> (-0.120,-0.031)
<b>Difference between treatments, LS-mean (95% CI)</b>	<b>-0.025</b> (-0,069,-0,020)	
<b>% of patients with an HbA1c level <math>&lt;</math> 6.5% after 52 weeks</b>	<b>29.1%</b> (n = 111/382)	<b>29.2%</b> (n =120/411)
<b>Difference between treatments (95% CI)</b>	<b>-0.1%</b> (-6.4 ; 6.2 )	

LS: least squares

\* on the per protocol population

### For the primary endpoint:

No difference was observed between the two treatments as regards the reduction in HbA1c levels.

### For the secondary endpoints:

No difference in reduction of the fasting blood glucose level and the percentage of patients with an HbA1c level  $<$  6.5% after 52 weeks was observed between the two treatments.

### Other endpoints established a posteriori:

The coefficient of durability was calculated. This coefficient represents the slope of the HbA1c variation curve from the 24th to the 52nd week. No conclusions can be drawn from this analysis.

### **3.3 Other data**

Indirect comparisons with glitazones have been submitted by the manufacturer:

- metformin+sitagliptin vs metformin $\geq$ 1500 mg/day (trial 020) and rosiglitazone/metformin vs metformin  $\geq$  3000 mg/day<sup>16</sup>
- metformin+sitagliptin vs metformin+glipizide (trial 024) and metformin+pioglitazone vs metformin+gliclazide<sup>17</sup>

These indirect comparisons cannot be taken into account by the Committee insofar as the doses of metformin evaluated differ between the studies, as do the characteristics of the populations included and analysed (especially the mean baseline HbA1c levels).

### **3.4 Adverse effects**

#### **3.4.1 Patients exposed/not exposed**

In the stage II/III pooled trials, 3,832 patients received sitagliptin<sup>18</sup>; 2,786 of them received a dose of 100 mg/day, and 2,355 a placebo or another treatment.

The adverse events most frequently observed in the population exposed to sitagliptin compared with the unexposed population were:

- infections: 76 vs. 74.8 events per 100 patient-years
- gastrointestinal disorders: 41.8 vs. 39.1 events per 100 patient-years
- rheumatological and connective tissue diseases: 32.6 vs. 31.5 events per 100 patient-years.

The frequency of blood and lymphatic disorders, which was highest in the group exposed to sitagliptin 100 mg/day (0.9% versus 0.3%, 1.5 versus 0.6 events per 100 patient-years), was basically due to anaemia and iron deficiency.

The adverse events observed with the highest frequency<sup>19</sup> in the group exposed to sitagliptin 100 mg were: upper abdominal pain, dyspepsia, shivering, bronchitis, rhinopharyngitis, tooth abscesses, meniscal damage, osteoarthritis, nasal congestion and contact dermatitis.

The European Risk Management Plan includes more detailed monitoring of gastrointestinal disorders, infections, neurological, psychiatric disorders (depression, suicide ideation/suicide), rheumatological and skin disorders.

#### **3.4.2 In combination with metformin**

**Trial 020:** sitagliptin/metformin vs. placebo/metformin

**Discontinuance of treatments:** six patients in the sitagliptin group (1.3%) discontinued their treatment due to the following adverse effects<sup>20</sup>: rash, urticaria, drowsiness, nausea/dizziness, increase in serum creatinine (2 patients). No discontinuance occurred in the placebo group.

**Adverse effects**<sup>21</sup>: observed in 9.3% of patients in the sitagliptin group and 10.1% of the patients in the placebo group. The most frequent adverse effects<sup>22</sup> in the patients treated with sitagliptin were nausea (1.1% vs. 0.4%), upper abdominal pain (0.9% vs. 0.4%), diarrhoea (0.6% versus 0%), reduced blood glucose level (0.4% versus 0%) and drowsiness (0.4% versus 0%).

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16 Bailey CJ, et al. Rosiglitazone/metformin fixed-dose combination compared with uptitrated metformin alone in type 2 diabetes mellitus: a 24-week, multicenter, randomized, double-blind, parallel-group study. Clin Ther. 2005 Oct;27(10):1548-61.

17 Matthews DR, et al. Long-term therapy with addition of pioglitazone to metformin compared with the addition of gliclazide to metformin in patients with type 2 diabetes: a randomized, comparative study. Diabetes Metab Res Rev 2005;21(2):167-174

18 590 at the dose of < 100 mg/day, and 456 at the dose of > 200 mg/day

19 CI of the difference between the 2 exposed or unexposed groups not including 0

20 considered to be associated with the treatment, due to clinical events or abnormal biological results

21 adverse drug reactions: considered to be associated with the treatment, for clinical events or abnormal biological results

22 inter-group difference >0.2% and > 1 patient)

Hypoglycaemia: 1.3% of patients in the sitagliptin group (6 patients/13 episodes) and 2.1% of patients in the placebo group (5 patients/6 episodes) had at least one episode of symptomatic hypoglycaemia. None of them was considered severe by the investigator.

Weight variation: a similar weight loss was observed in both groups (about - 0.7 kg)<sup>23</sup>.

**Trial 024**: sitagliptin/metformin vs. glipizide/metformin

Discontinuance of treatments: 11 patients in the sitagliptin group (2%) and 10 patients in the glipizide group (2%) discontinued their treatment due to the following adverse effects:

- In the sitagliptin group: asthenia, cough, generalised urticaria, dyspepsia, hyperkalaemia, drowsiness, type II atrioventricular blockade, polymyalgia, benign tumours of the salivary glands, increase in ALAT/ASAT (2),
- In the glipizide group: hypoglycaemia (3), diarrhoea (2), increase in ALAT/ASAT (2), hypersensitivity, urticaria, constipation/dizziness.

Adverse effects: 14.5% of adverse reactions associated with the treatment were observed in the sitagliptin group, and 30.3% in the glipizide group.

Hypoglycaemia: 4.9% of the patients in the sitagliptin group (29/588 patients, 50 episodes) and 32.0% of the patients in the glipizide group (187/584, 657 episodes) had at least one episode of hypoglycaemia<sup>24</sup>. According to the trial protocol, it was symptomatic hypoglycaemia, without systematic measurement of the blood glucose level.

Two episodes of hypoglycaemia in two patients in the glipizide group were considered severe by the investigator, and none in the sitagliptin group. Four patients in the glipizide group discontinued their treatment.

Weight variation: a weight reduction was observed in the sitagliptin group (-1.5 kg, mean baseline weight 89.4 kg), while a weight increase was recorded in the glipizide group (+ 1.1 kg, mean baseline weight 89.5 kg)<sup>25</sup>.

### **3.4.3 In combination with a PPAR $\gamma$ receptor agonist (pioglitazone)**

**Trial 019**: sitagliptin/pioglitazone vs. placebo/pioglitazone

Discontinuance of treatments: one patient in the sitagliptin group due to angioneurotic oedema and one patient in the placebo group due to peripheral oedema.

Adverse effects: observed in 9.1% of patients in the sitagliptin group and 9.0% of patients in the placebo group; the adverse reactions most frequently observed<sup>26</sup> in the patients treated with sitagliptin were hypoglycaemia (1.1% vs. 0%) and flatulence (1.1% vs. 0%)<sup>27</sup>.

Weight variation: a similar weight gain was observed in the two treatment groups (+1.5 to +1.8 kg)<sup>28</sup>

## **3.5 Conclusion**

The efficacy of sitagliptin in combination with metformin or pioglitazone was evaluated in patients suffering from type 2 diabetes poorly controlled by metformin alone, at a stable dose  $\geq$  1500 mg/day (trials 020 and 024), or by pioglitazone alone, at the dose of 30 mg/day or 45 mg/day (trial 019). Patients suffering from moderate to severe kidney failure were excluded from these 3 trials.

23 mean baseline weight 86.9 kg in the sitagliptin group and 87.6 kg in the placebo group

24 patient incidence  $\Delta$  = -27.0% 95% CI [-31.2% ; -22.9%], p<0.001

25 least-squares mean,  $\Delta$  between treatments: -2.5 kg, 95% CI [-3.1;-2.0] p < 0.001 according to the ANCOVA model

26 intergroup difference >0.2% and > 1 patient

27 2 oedemas considered to be associated with the treatment were also observed in each group

28 mean baseline weight 90 kg in the sitagliptin group and 85.6 kg in the placebo group.

In combination with metformin, in placebo-controlled trial 020, after 24 weeks' treatment, the reduction in HbA1c level (mean baseline HbA1c level 8%) was greater in the group of patients treated with the combination metformin+sitagliptin than in the group treated with metformin alone: -0.67% vs. -0.02% (difference between treatments of 0.65%, 95% CI (-0.77,-0.53)  $p < 0.001$ ).

In trial 024 vs. glipizide (sulphonylurea), after 52 weeks' treatment, the combination metformin+sitagliptin was not inferior to the combination metformin+glipizide in reducing the HbA1c level (-0.67% in both groups) in patients poorly controlled (mean baseline level of 7.5%) by metformin treatment at a stable dose  $\geq 1500$  mg/day. However, the evidence level of this non-inferiority trial is not optimal in view of the non-maximum doses of glipizide used and the discontinuances of the treatment due to inefficacy, which were more frequent in the metformin+sitagliptin group than in the metformin + glipizide group.

In combination with pioglitazone, in placebo-controlled trial 019, after 24 weeks' treatment, the reduction in HbA1c level (mean baseline HbA1c level 8%) was greater in the group of patients treated with the combination pioglitazone + sitagliptin than in the group treated with pioglitazone alone, at the dose of 30 mg/day or 45 mg/day: -0.85% vs. -0.15% (difference between treatments of -0.70% (95% CI [-0.85,-0.54]  $p < 0.001$ ).

In terms of safety, in combination with metformin, in placebo-controlled trial 020, the adverse reactions most frequently observed in the sitagliptin group were nausea, upper abdominal pain, diarrhoea, reduced blood glucose level, and drowsiness.

In combination with pioglitazone, in placebo-controlled trial 019, the adverse reactions most frequently observed in the sitagliptin group were hypoglycaemia and flatulence.

The number of episodes of symptomatic hypoglycaemia was similar in the placebo and sitagliptin groups of trials 020 and 019.

Moreover, in trial 024, the combination metformin/sitagliptin caused fewer episodes of symptomatic hypoglycaemia than the combination of metformin/glipizide.

Weight variations with sitagliptin were similar to those observed with the placebo in trials 020 and 019. Conversely in trial 024, a weight loss was observed with the combination metformin/sitagliptin, while a weight increase was recorded with the combination of metformin/glipizide.

In the context of the European Risk Management Plan, infections, gastrointestinal disorders, rheumatological and neuropsychiatric disorders require special monitoring.

The combination metformin+sitagliptin was only evaluated by comparison with the combination metformin + sulphonylurea. The Committee has no other direct comparisons which would allow the benefits of the combination metformin+sitagliptin vs. other bitherapies, especially metformin+glitazone, to be quantified.

No data from controlled trials comparing the combination pioglitazone + sitagliptin with another bitherapy are available. The Committee therefore does not have data which would enable it to quantify the benefits of the new combination glitazone+sitagliptin compared with other bitherapies.

The use of sitagliptin in tritherapy (metformin + sitagliptin + another hypoglycaemic agent or pioglitazone + sitagliptin + another hypoglycaemic agent) was not evaluated.

No data which would enable sitagliptin to be evaluated by comparison with insulin are available.

## 4. TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1. Actual benefit

Type 2 diabetes is a chronic disorder with potentially serious complications.

JANUVIA is classed as a treatment for hyperglycaemia.

The efficacy/adverse effects ratio of JANUVIA is high.

There are alternative medications to this product.

JANUVIA is an additional therapeutic aid for the treatment of type 2 diabetics.

Public health benefit:

Type 2 diabetes represents a major public health burden. The burden corresponding to the sub-population of patients liable to benefit from JANUVIA is moderate.

Improving the treatment of type 2 diabetes is an established public health need.

The available data do not permit the impact of JANUVIA on blood glucose control and morbidity/mortality compared with the currently available oral bitherapies to be estimated. The response provided by Januvia to the public health need cannot be evaluated on the basis of the current state of knowledge.

There is also no guarantee that experimental data will be transposed into clinical use.

Consequently, no public health benefit is forecast for JANUVIA.

The actual benefit of JANUVIA is substantial.

### 4.2. Improvement in actual benefit

JANUVIA provides a minor improvement in actual benefit (IAB IV) in the management of type 2 diabetes in patients treated with metformin in monotherapy, if diet, physical exercise and metformin do not achieve sufficient control of the blood glucose level.

### 4.3. Therapeutic use

The objectives of therapy are:

- Blood glucose control: control of HbA1c,
- Control of associated risk factors.

According to the guideline "Medical treatment of type 2 diabetes" published by Afssaps and HAS in November 2006, the initial treatment of type 2 diabetes is based on evaluation and realistic modification of the patient's lifestyle (diet and physical exercise). An active campaign against a sedentary lifestyle and nutritional planning are essential interventions at all stages of management of this disorder.

Oral antidiabetics should be introduced when diet and lifestyle measures (DLM) are no longer sufficient to control the blood glucose level: HbA1c > 6%. There are 4 therapeutic classes: metformin, intestinal alphasglucosidase inhibitors (IAG), insulin secretors and glitazone.

The various stages of treatment are described in table 4 below.

**Table 4 - Treatment strategy (LTI 8 - Type 2 diabetes)<sup>29</sup>**

Baseline HbA1c	Treatment	HbA1c target
HbA1c between 6% and 6.5% despite DLM	Monotherapy with metformin (or IAG in the event of intolerance or contraindication)	< 6.5%
HbA1c > 6.5% despite DLM	Monotherapy with metformin or insulin secretor or IAG	Maintain HbA1c < 6.5%
HbA1c > 6.5% despite monotherapy and DLM	Bitherapy	Reduce HbA1c < 6.5%
HbA1c > 7% despite bitherapy and DLM	- Tritherapy: metformin + insulin secretor + glitazone or - insulin + metformin ± other OADs except for glitazone	Reduce HbA1c < 7%
HbA1c > 8% despite tritherapy and DLM	Insulin + metformin ± other OADs except for glitazone	Reduce HbA1c < 7%

DLM: dietary and lifestyle measures; ADO: oral antidiabetics; IAG: intestinal alphasglucosidase inhibitors

#### The role of JANUVIA:

Within its therapeutic indication, the Transparency Committee considers that JANUVIA should be used mainly in combination with metformin if diet, physical exercise and metformin do not achieve sufficient control of the blood glucose level (HbA1c > 6.5% despite lifestyle and dietary measures and monotherapy with metformin).

The Committee took into account the fact that glitazones have a limited role in monotherapy. As no data from controlled trials comparing the combination pioglitazone + sitagliptin with another bitherapy are available, the Committee does not have data enabling it to position this new glitazone+sitagliptin bitherapy in relation to the other available bitherapies.

JANUVIA should not be used in patients with moderate to severe kidney failure.

#### **4.4. Target population**

According to the indication stated in the MA, the target population of JANUVIA corresponds to type 2 diabetics treated:

- with metformin if diet, physical exercise and metformin do not provide adequate control of the blood glucose level, or
- with a PPAR $\gamma$  receptor agonist (thiazolidinedione) if appropriate, and if this treatment, used in monotherapy with diet and physical exercise, does not adequately control the blood glucose level.

<sup>29</sup> Management of diabetes: Type 2 diabetes. Doctors' guidelines - Long-Term Illness, HAS - May 2006

The data of the trial conducted with the permanent sample of persons who pay social security contributions (EPAS) set up by the National Health Insurance Fund for Salaried Workers (CNAMTS)<sup>30</sup> indicate that the prevalence of diabetes treated in metropolitan France (all schemes) was 3.8% in 2005, and the mean annual increase recorded between 2000 and 2005 was 5.7%. On the basis of these percentages, and assuming that the mean annual increase recorded between 2000 and 2005 was the same between 2005 and 2006, the number of diabetics treated in 2006 was approximately 2,472,000<sup>31</sup>.

Ninety one% of them were type 2 diabetics (ENTRED 2001-2003 - diabetes network no. 29 - September 2006).

According to the results of the ECODIA 2 trial, published in part (Diabetes network no. 31 - March 2007):

- 83.2% of type 2 diabetics are treated with oral antidiabetics without insulin; 24% of them are treated in monotherapy with metformin, and 1.5% in monotherapy with glitazone.
- 68% of the patients have an HbA1c level exceeding 6.5%.

The population of patients unresponsive to correctly conducted monotherapy with metformin is therefore 305,000, and the number of patients unresponsive to correctly conducted monotherapy with glitazone (pioglitazone or rosiglitazone) is 19,000, corresponding to the indications in the JANUVIA MA of about 324,000 patients.

The population of patients most likely to benefit from JANUVIA corresponds to patients treated with metformin who did not achieve adequate blood glucose control. This would represent a total of about 305,000 patients.

The Committee rules that JANUVIA must not be used in patients with moderate to severe kidney failure.

The above-mentioned population is therefore a broad estimate, having regard to the probable existence of metformin prescriptions for patients with unidentified kidney failure. However, that population is not quantifiable.

Consequently, the Transparency Committee considers that the population of patients most likely to benefit from JANUVIA, namely the IACB population, corresponds to patients correctly treated with metformin who have not achieved adequate blood glucose control, amounting to a maximum of 305,000 patients.

#### **4.5. Transparency Committee recommendations**

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance (box of 28 and 50) and on the list of medicines approved for use by hospitals and various public services (box of 50) in the marketing authorisation.

The Transparency Committee requests a trial be conducted on a representative sample of type 2 diabetics, in France, treated with JANUVIA. This trial should describe the following aspects under actual treatment conditions:

- the characteristics of the patients treated (including age, baseline HbA1c level, kidney function, etc.);
- the conditions of use of this proprietary product (indication, dose and dosage adjustments, concomitant treatments, blood glucose monitoring procedures, etc.);
- the compliance rate for the treatment;
- the frequency of discontinuations and the reasons for them;
- the clinical course of HbA1c, and the onset of hypoglycaemia, in the long term (2 years).

The duration of the trial, determined by a scientific committee, must be justified and sufficient to answer the questions of the Transparency Committee.

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30 Diabète traité, quelles évolutions entre 2000 et 2005, Prat Organ Soins 2007; 38 (1):1-12

31 on the basis of the INSEE (French National Statistics and Studies Institute) population as at 1 January 2007

If the studies planned or in progress, especially in the context of the European Risk Management Plan, are unable to answer all the questions asked by the Transparency Committee, a specific trial must be conducted.

#### 4.5.1 Packaging

In accordance with its resolution dated 20 July 2005, the Committee recommends a standardised 30-day pack for one-month treatments.

#### 4.5.2 Reimbursement rate: 65%