HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

24 June 2009

JANUVIA 100 mg, film-coated tablets
B/28 (CIP code: 379 250-4)
B/50 (CIP code: 570 745-4)

Applicant: MERCK SHARP & DOHME-CHIBRET

sitagliptin
ATC code: A10BH01

List I

Date of the Marketing Authorisations (centralised procedure): 21 March 2007
Date of extensions of indication (centralised procedure): 26 February 2008

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 patients with type 2 diabetes mellitus, JANUVIA is indicated 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.

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

Medical, Economic, and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

sitagliptin

1.2. 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. *(indication already assessed by the TC, see opinion dated 6 June 2007)*

- **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.**

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

In type 2 diabetics for whom the use of a PPARγ receptor agonist (thiazolidinedione) is appropriate, JANUVIA is indicated:

- in combination with this PPARγ receptor agonist, when diet and exercise plus this substance alone do not provide adequate glycaemic control". *(indication already assessed by the TC, see opinion dated 6 June 2007)*

1.3. Dosage

"The dose of JANUVIA is 100 mg once daily. When sitagliptin is used in combination with metformin and/or a PPARγ receptor agonist, the dose of metformin and/or PPARγ receptor agonist should be maintained.

When JANUVIA is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia.

If a dose of JANUVIA is missed, it should be taken as soon as the patient remembers. A double dose should not be taken the same day.

JANUVIA may be taken with or without food.

Patients with renal insufficiency

No dose adjustment of JANUVIA is required in patients with mild renal impairment (creatinine clearance [CrCl] ≥ 50 ml/min).

Clinical study experience with JANUVIA in patients with moderate or severe renal impairment is limited. Therefore, use of JANUVIA is not recommended in this population.

Patients with hepatic insufficiency

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 according to age. Limited tolerance data is available in patients ≥ 75 years. Prudence is therefore necessary.

Paediatric population

JANUVIA is not recommended for use in children below 18 years of age due to a lack of data on its tolerance and efficacy. »

1.4. Special warnings and precautions for use (see SPC)[1]

"Hypoglycaemia when used in combination with other anti-hyperglycaemic agents

In clinical trials of JANUVIA as monotherapy and as part of combination therapy with agents not known to cause hypoglycaemia (i.e. metformin or pioglitazone), rates of hypoglycaemia reported with sitagliptin were similar to rates in patients taking placebo. When sitagliptin was added to a sulphonylurea, the incidence of hypoglycaemia was increased over that of placebo. **Therefore, to reduce the risk of hypoglycaemia, a lower dose of sulphonylurea may be considered.** The use of sitagliptin in combination with insulin has not been sufficiently investigated.

Renal impairment

As experience is limited, patients with moderate to severe renal impairment should not be treated with JANUVIA.

Hypersensitivity reactions

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

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

A	Alimentary tract and metabolism
A10	Drugs used in diabetes
A10B	Blood glucose lowering drugs, excl. insulins
A10BH	dipeptidyl peptidase-4 (DPP-4) inhibitors
A10BH01	sitagliptin

2.2. Medicines in the same therapeutic category

- XELEVIA 100 mg, tablets (sitagliptin), indicated "for type 2 diabetics to improve glycaemic control:

  - in combination with metformin, when diet and exercise plus metformin alone do not provide adequate glycaemic control. *(indication already assessed by the TC, see opinion dated 19.12.07)*
  - 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.
  - in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.

In type 2 diabetics for whom the use of a PPARγ receptor agonist (thiazolidinedione) is appropriate, XELEVIA is indicated in combination with this PPARγ receptor agonist where this substance alone, in combination with diet and exercise, does not provide adequate glycaemic control". *(indication already assessed by the TC, see opinion dated 19.12.07)*

[1] The warnings and precautions for use associated with the use of vildagliptin (GALVUS), particularly in the case of hepatic or cardiac impairment, are not found in the SPC for sitagliptin (JANUVIA).

- GALVUS 50 mg, tablets (vildagliptin)**,** indicated "in the treatment of type 2 diabetes, as oral bitherapy, in combination with:
- metformin, in patients whose glycaemia is inadequately controlled despite taking a maximum safe dose of metformin as monotherapy,
- a sulphonylurea, in patients whose glycaemia is inadequately controlled despite taking a maximum safe dose of sulphonylurea and for whom metformin is not appropriate due to intolerance or a contraindication,
- a thiazolidinedione, in patients whose glycaemia is inadequately controlled and for whom the use of a thiazolidinedione is appropriate."

(proprietary medicine not yet included on the list of proprietary medicines refundable by National Health Insurance or on the list of proprietary medicines approved for use by hospitals, see the transparency Committee's opinion dated 10 December 2008)
N.B.: GALVUS is not indicated for use in oral tritherapy

2.3. Medicines in the same therapeutic category

- in oral bitherapy, in combination with a sulphonylurea:

- in type 2 diabetics who have not achieved adequate glycaemic control at the maximum safe doses of an oral sulphonylurea-based monotherapy and for whom metformin is contraindicated or poorly tolerated:
    - glitazones
    - intestinal alpha-glucosidase inhibitors
    - injectable incretin mimetic, exenatide (BYETTA)

- as oral tritherapy: in combination with metformin and a sulphonylurea in type 2 diabetic patients whose glycaemia is inadequately controlled by metformin and sulphonylurea bitherapy at the maximum safe doses:
    - glitazones
    - insulin
    - injectable incretin mimetic

3. ANALYSIS OF AVAILABLE DATA

The extensions of indications to include oral bitherapy and tritherapy were validated by the registration authorities on the basis of a phase III, comparative, randomised double-blind study (study 035[2]), the primary aim of which was to demonstrate the efficacy and tolerance of sitagliptin in combination with a sulphonylurea (glimepiride) alone or in combination with metformin compared with placebo after 24 weeks of treatment in 441 patients with type 2 diabetes that was insufficiently controlled (HbA1c ≥7.5% and ≤10.5%) by monotherapy with glimepiride (at a dose ≥ 4 mg/d) or bitherapy with glimepiride and metformin (at doses of ≥ 4 mg/d and ≥ 1,500 mg/d respectively).

This study (phase A) was followed by another treatment phase (phase B) lasting 30 weeks versus an active comparator (pioglitazone), the main aim of which was to assess the tolerance of sitagliptin.
The protocol specified that during phase B:

- patients who were on sitagliptin in phase A continued their treatment with sitagliptin + glimepiride ± metformin
- patients who were on placebo in phase A were given active treatment: pioglitazone 30 mg/day plus glimepiride ± metformin.

Patients randomised to the placebo group in phase A were treated with pioglitazone in phase B. There was no new randomisation and the treatments in this phase did not start at the same time. The two treatment groups are therefore not comparable, selection bias existed, and no comparison could be made (the effect of treatment could not be assessed). Moreover, the study protocol indicates that no hypothesis was formulated for this phase.
The efficacy of sitagliptin versus an active comparator cannot therefore be assessed.

This document only describes the **results of phase A** of the study (i.e. versus placebo).

Methodology:
Double-blind, randomised, placebo-controlled phase III study.

The protocol specified stratified randomisation according to the type of treatment received: glimepiride alone or glimepiride + metformin.
This study therefore compared two strata:

- stratum 1: assessment of glimepiride + sitagliptin bitherapy versus glimepiride + placebo
- stratum 2: assessment of glimepiride + metformin + sitagliptin tritherapy versus glimepiride + metformin + placebo.

Inclusion criteria:
Patients with type 2 diabetes, aged from 18 to 75, insufficiently controlled (HbA1c ≥7.5% and ≤10.5%) by fixed-dose glimepiride monotherapy (≥ 4 mg/d) or bitherapy involving fixed-dose glimepiride (≥ 4 mg/d) + fixed-dose metformin (≥ 1,500 mg/d) for 10 weeks.

2 Hermansen K, Kipnes M, Luo E, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. Diabetes Obes Metab 2007;9(5):733-745

Administration regimen:
Four hundred and forty-one patients[3] were randomised to receive:

- in stratum 1 (n=212): either sitagliptin at a dose of 100 mg once daily + glimepiride at a fixed dose of ≥ 4 mg/d once daily (n=106) or placebo + glimepiride (n=106)
- in stratum 2 (n=229): either sitagliptin at a dose of 100 mg once daily + glimepiride at a fixed dose of ≥ 4 mg/d once daily + metformin at a fixed dose of ≥ 1,500 mg/day twice daily (n=116) or placebo + glimepiride + metformin (n=113).

Primary efficacy endpoint:
Average variation in HbA1c after 24 weeks of treatment compared to the baseline value for the total study population

The protocol specified the following inclusion rates:

- 172 patients in the two treatment groups in order to demonstrate a difference of 0.5% ± 1.0% in respect of the variation in the HbA1c level with a power of 99% and an overall significance level of 0.05.
- 86 patients in each treatment group in both strata in order to demonstrate a difference of 0.5% ± 1.0% in respect of the variation in the HbA1c level with a power of 90% and an overall significance level of 0.05.

Analyses were performed for this primary efficacy endpoint. They were specified in the protocol and carried out in sub-groups of patients (based on their previous blood lipid lowering treatment, the initial HbA1c level of <8% and ≥9%, BMI, and the length of time that the patient had had diabetes). As no adjustment method was applied to take account of multiple comparisons, the possibility of an overestimation of the effect cannot be ruled out. Consequently, no conclusions can be drawn on the basis of these exploratory analyses, and they are therefore not presented.

Secondary endpoints:

- average variation in HbA1c levels in bitherapy (in stratum 1)
- average variation in HbA1c levels in tritherapy (in stratum 2)
- average variation in fasting glycaemic levels in the total study population and in each stratum

N.B.: a method for checking significance level inflation resulting from multiple comparisons was applied in the assessment of these criteria in order to avoid overestimating the observed effect

Other criteria defined a posteriori:
Fasting insulin and proinsulin, proinsulin/insulin ratio, C-peptide, HOMA-β[4], HOMA-IR[2] QUICKI[5], percentage of patients with an HbA1c level <6.5% and <7%, percentage of patients requiring rescue treatment[6] and time taken to administer it, lipid profile.
The findings for these endpoints will not be described as their analysis was purely exploratory.
However, the results for the endpoint "percentage of patients with an HbA1c level <6.5% and <7%" will be presented as they relate to the aims of treatment. It is unfortunate that this clinically relevant criterion was not subjected to a more robust analysis.

[3] 222 on sitagliptin, 219 on placebo
4 Insulin resistance was assessed using the homeostasis model
5 Quantitative insulin resistance index
6 in the form of pioglitazone 30 mg/day

3.1. Efficacy results

The results were obtained from analysis of all patients who were randomised and received at least one dose of treatment.

The characteristics of patients in the overall study population were similar on inclusion. They were:
- aged 56 on average (20% of patients were 65 or over),
- in most cases obese (average BMI of 31.0 kg/m^2).

They had had diabetes for 8.8 years on average.
The average HbA1c level on inclusion was 8.34%. Most of the patients (44.7%) had an HbA1c level between 8 and 9%. It should be noted that HbA1c levels on inclusion were high.

Table 1: characteristics of the total study population

Age (years)				
	N	Mean + SD	Median	Extremes
Sitagliptin	222	55.6 + 9.6	56.0	32.0 to 73.0
Placebo	219	56.5 + 9.6	58.0	28.0 to 75.0
Overall	441	56.0 + 9.6	57.0	28.0 to 75.0
Body mass index (kg/m²)				
	N	Mean + SD	Median	Extremes
Sitagliptin	221	31.2 + 6.3	30.4	17.8 to 51.0
Placebo	219	30.7 + 6.3	29.3	19.6 to 59.2
Overall	440	31.0 + 6.3	29.8	17.8 to 59.2
HbA1c level (%)				
	N	Mean + SD	Median	Extremes
Sitagliptin	222	8.34 + 0.76	8.20	6.70 to 10.50
Placebo	216	8.34 + 0.74	8.25	6.90 to 10.60
Overall	438	8.34 + 0.75	8.20	6.70 to 10.60
Distribution of HbA1c				
	N	Number (%) of patients with HbA1c on inclusion		
		<8%	≥8 and <9%	≥9%
Sitagliptin	222	81 (36.5)	95 (42.8)	46 (20.7)
Placebo	216	73 (33.8)	101 (46.8)	42 (19.4)
Overall	438	154 (35.2)	196 (44.7)	88 (20.1)
Fasting glycaemia (mg/dL)				
	N	Mean + SD	Median	Extremes
Sitagliptin	222	180.9 + 37.7	178.0	76.0 to 281.0
Placebo	217	181.6 + 42.5	180.0	85.0 to 295.0
Overall	439	181.2 + 40.1	179.0	76.0 to 295.0
Duration of type 2 diabetes (years)				
	N	Mean + SD	Median	Extremes
Sitagliptin	222	8.3 + 5.5	7.0	0.3 to 30.0
Placebo	218	9.3 + 6.8	8.0	0.1 to 43.0
Overall	440	8.8 + 6.2	8.0	0.1 to 43.0
Blood lipid lowering treatments				
	Combination of OADs* N (%)	Monotherapy N (%)	No treatment N (%)	Total N
Sitagliptin	140 (63,1)	71 (32.0)	11 (5.0)	222
Placebo	136 (62,1)	72 (32.9)	11 (5.0)	219
Overall	276 (62,6)	143 (32.4)	22 (5.0)	441

* OADs: oral antidiabetics

The characteristics of the patient population in stratum 1 (bitherapy stratum) were:
- average age 54.8 ± 10.3 years, with 17% of patients aged 65 or over,
- BMI of 30.9 ± 6.5 kg/m^2,
- average HbA1c level of 8.43 ± 0.79% (33% of patients had a level < 8%, 42% between 8 and 9% and 25% of patients had a level of ≥ 9%),
- average baseline fasting glycaemia of 1.84 ± 0.38 g/L,

- duration of diabetes of 7.6 ± 5.8 years,
- 9% of patients were receiving no treatment, 63.7% of patients were receiving monotherapy and 27.4% of patients were receiving a combination of oral antidiabetics.

The characteristics of the patient population in stratum 2 (tritherapy stratum) were:

- average age 57.1 ± 8.8 years, with 23% of patients aged 65 or over,
- BMI of 31.0 ± 6.0 kg/m^2,
- average HbA1c level of 8.26 ± 0.70% (37.2% of patients had a level < 8%, 47.3% had a level between 8 and 9% and 15.5% of patients had a level of ≥ 9%),
- average baseline fasting glycaemia of 1.79 ± 0.42 g/L,
- duration of diabetes of 9.9 ± 6.3 years,
- 1.3% of patients were receiving no treatment, 3.5% of patients were receiving monotherapy and 95.2% of patients were receiving a combination of oral antidiabetics.

N.B.: the characteristics of patients included were the same in each treatment group, whether in the total population or within each stratum, except in stratum 2 (tritherapy) where the HbA1c level was lower than in stratum 1 (bitherapy), patients had had diabetes for longer and more patients had previously been treated with combination oral antidiabetics (OADs).

Primary efficacy endpoint:

Table 2: change in HbA1c levels after 24 weeks in the total population:

Treatment group	**N**	**Mean initial HbA1c level (standard deviation)**	**Adjusted mean change in HbA1c levels (SD), 95% CI**	**Mean difference versus comparator, 95% CI**
glimepiride ± metformin + sitagliptin	217	8.34 (0.76)	-0.45 (0.06) [-0.57. -0.34]	**- 0.74** **[-0.90 ;-0.57]** **p<0.001**
glimepiride ± metformin + placebo	208	8.37 (0.74)	0.28 (0.06) [0.17 ; 0.40]	

After 24 weeks of treatment, the reduction in HbA1c was greater among patients taking glimepiride **+** metformin + sitagliptin than among those taking glimepiride **+** metformin + placebo (difference between sitagliptin and placebo: -0.74%, 95%CI [-0.90; -0.57]; p<0.001).

It should be noted that sitagliptin was most effective up to the 12th week of treatment. HbA1c levels rose after that point.

Secondary endpoints:

- Mean change in HbA1c levels in bitherapy (in stratum 1): table 3

Treatment group	N	Mean initial HbA1c level (standard deviation)	Adjusted mean change in HbA1c levels (SD), 95% CI	Mean difference versus comparator, 95% CI
glimepiride + sitagliptin	102	8.41 (0.78)	-0.30 (0.09) [-0.48 ; -0.12]	**- 0.57** **[-0.82 ; -0.32**] **p<0.001**
glimepiride + placebo	103	8.46 (0.80)	0.27 (0.09) [0.09 ; 0.45]	

- Mean change in HbA1c levels in tritherapy (in stratum 2): table 4

Treatment group	N	Mean initial HbA1c level (standard deviation)	Adjusted mean change in HbA1c levels (SD), 95% CI	Mean difference versus comparator, 95% CI
glimepiride ± metformin + sitagliptin	115	8.27 (0.74)	-0.59 (0.08) [-0.74 ; -0.44]	**- 0.89** **[-1.10 ;-0.68**] **p<0.001**
glimepiride + metformin + placebo	105	8.28 (0.68)	0.30 (0.08) [0.14 ; 0.45]	

A statistically significant reduction in the HbA1c level was observed in oral bitherapy[7] and tritherapy. However, this fall lasted only for the first 12 weeks of treatment, after which point HbA1c levels rose.

- Mean change in fasting glycaemic levels in the total study population and in each stratum:

After 24 weeks of treatment, the fall in fasting glycaemia levels was greater among patients in the glimepiride ± metformin + sitagliptin group than among those in the glimepiride ± metformin + placebo group.

Treatment group	Total population	Stratum 1	Stratum 2
sitagliptin	-4.4 [-10.2 ; 1.4]	-0.9 [-9.8 ; 8.0]	-7.8 [-15.5 ; -0.2]
placebo	15.7 [9.8 ; 21.6]	18.4 [9.5 ; 27.3]	12.9 [5.0 ; 20.8]
Difference versus placebo	-20.1 [-28.4 ; -11.8] p < 0. 005	-19.3 [-31.9 ; -6.7] p < 0. 005	-20.7 [-31.7 ; -9.7] p < 0. 005

Criterion defined a posteriori: percentage of patients with an HbA1c level <6.5% and <7% (exploratory analysis)

The aim during bitherapy is to bring HbA1c levels down to < 6.5%. In the bitherapy stratum, no difference was observed between the treatment groups at 24 weeks. The same result was seen in the analysis of the total population.

[7] Almost half of the difference in HbA1c levels observed (-0.57%) was linked to the rise in HbA1c levels in patients receiving placebo

In tritherapy, the aim of treatment is to achieve an HbA1c level of < 7%. A statistically significant difference in respect of whether or not the treatment aim was achieved was observed in the tritherapy stratum (26/115 patients in the sitagliptin group versus 1/105 patients in the placebo group, p<0.001) and in the total study population (37/217 patients in the sitagliptin group versus 10/208 patients in the placebo group, p <0.001).

3.2. Adverse effects

3.2.1. Tolerance data from study P035

In the total study population, 59.5% of patients in the sitagliptin group (132/222) and 47% of patients in the placebo group (103/219) experienced at least one adverse event.
The adverse events reported more frequently in the sitagliptin group than in the placebo group were:

- infections (mainly cases of rhinopharyngitis and upper respiratory tract infection): 31.1% of patients in the sitagliptin group versus 21.9% of patients in the placebo group
- metabolic disorders (mainly hypoglycaemia): 13.5% (30/222) versus 4.1% (9/219)
- musculo-skeletal disorders: 12.6% (28/222) versus 6.8% (15/219)
- central nervous system disorders (mainly headaches): 10.4% (23/222) versus 5% (11/219).

The same events were reported in each stratum.

Cases of hypoglycaemia were observed in 27 patients in the sitagliptin group (55 hypoglycaemic episodes in total) and 4 patients in the placebo group (20 hypoglycaemic episodes in total). These hypoglycaemic episodes were reported most often in stratum 2 (42 hypoglycaemic episodes in 19 patients in the sitagliptin group versus 1 hypoglycaemic episode in 1 patient in the placebo group).
No cases of severe hypoglycaemia were observed.

The incidence of gastrointestinal adverse events (abdominal pain, nausea, vomiting, diarrhoea) was similar in both treatment groups (28/222 patients in the sitagliptin group, 24/219 patients in the placebo group).
After 24 weeks of treatment, weight gain among patients in the sitagliptin group amounted to 0.8 kg, compared to weight loss of 0.4 kg among patients in the placebo group (a difference of 1.1 kg 95% CI [0.5; 1.7], p<0.001)[8]. This result was also observed in each stratum.

Discontinuation of treatment because of adverse effects occurred in the case of five patients in the sitagliptin group and three patients in the placebo group.

3.2.2. Tolerance data from the pooled analysis of tolerance data for all the clinical trials available[9]

This analysis included twelve studies (phase IIb and phase III) lasting between 18 weeks and two years, including patients treated with sitagliptin as monotherapy or in combination with metformin or another OAD (sulphonylurea, pioglitazone, metformin + sulphonylurea, metformin + rosiglitazone).
Patients in the "unexposed" comparator arms were on placebo, sulphonylurea, glitazone, or combinations of OADs (metformin + sulphonylurea, metformin + rosiglitazone, metformin + pioglitazone).
A total of 6,139 patients were included in the analysis: 3,415 in the groups on sitagliptin and 2,724 in the unexposed groups.

[8] The analysis was carried out on 178 patients in the sitagliptin group and 147 patients in the placebo group. Patients who had received rescue treatment were excluded from this analysis.
[9] Williams-Herman D et al. Safety and tolerability of sitagliptin in patients with type 2 diabetes: A pooled analysis *BMC Endocrine Disorders 2008, **8**:14 (in press)*

The incidence of adverse events attributable to treatment was higher in the group of "unexposed" patients, mainly because of cases of hypoglycaemia linked to sulphonylureas: 12.9% of patients in the sitagliptin group and 17.7% of "unexposed" patients.
The analysis of adverse events showed that there was no inter-group difference except for metabolic disorders. The difference was due mainly to a greater incidence of hypoglycaemia in the "unexposed" group (10.9%) compared to the sitagliptin group (3.4%). These effects were mainly seen in patients being treated with sulphonylureas.

3.2.3. Tolerance data obtained from the latest PSUR (covering the period from 4 February 2008 to 3 August 2008)

Analysis of the data from the latest international PSUR for JANUVIA produced results in line with the risk information mentioned in the current marketing authorisation. Tolerance is closely monitored in the context of the international RMP.
It should be noted that, in addition to the European RMP for JANUVIA, Afssaps has set up an enhanced national pharmacovigilance monitoring programme, focusing mainly on monitoring infectious disorders, gastrointestinal disorders, rheumatological conditions and neuro-psychiatric disorders.
No new signals have appeared, particularly in respect of hepatic or pancreatic disorders or in respect of drug interaction.

3.2.4. Post-marketing authorisation changes to the SPC of JANUVIA regarding tolerance

Since JANUVIA was placed on the market, the "warnings" section of the SPC has been updated in relation to hypersensitivity reactions (anaphylaxia, angio-oedema, rash, urticaria and exfoliative skin lesions, including Stevens-Johnson syndrome).

3.3. Conclusion

The assessment of the efficacy and tolerance of sitagliptin in oral bitherapy and oral tritherapy (in combination with a sulphonylurea, glimepiride, alone or in combination with metformin) is based on a phase III, comparative, placebo-controlled, randomised, double-blind study lasting 24 weeks carried out on 441 patients with type 2 diabetes inadequately controlled (HbA1c level ≥7.5% and ≤10.5%) by monotherapy with glimepiride (at a dose of ≥ 4 mg/d) or bitherapy with glimepiride and metformin (at doses of ≥ 4 mg/d and ≥ 1500 mg/d respectively).
This study was followed by another treatment phase lasting 30 weeks versus an active comparator (pioglitazone), the main aim of which was to assess the tolerance of sitagliptin. The efficacy of sitagliptin versus the active comparator in this phase cannot be assessed as a result of the methodological shortcomings (existence of selection bias, no hypothesis formulated).
The first phase of this study included 2 strata: stratum 1, assessing glimepiride + sitagliptin bitherapy versus sitagliptin + placebo, and stratum 2, assessing metformin + glimepiride + sitagliptin tritherapy versus metformin + glimepiride + placebo.
The characteristics of patients included were the same in each treatment group, whether in the total population or within each stratum, except in stratum 2 (tritherapy) where the HbA1c level was lower than in stratum 1 (bitherapy), patients had had diabetes for longer and more patients had previously been treated with combination oral antidiabetics.

- **In terms of efficacy,** after 24 weeks of treatment, the fall in HbA1c levels (primary efficacy endpoint) was -0.74%, 95% CI [-0.90; -0.57]; p<0.001 in patients on glimepiride ± metformin + sitagliptin compared to patients on glimepiride ± metformin + placebo.

This level of efficacy is similar to that of a meta-analysis[10] of 29 trials conducted to assess the efficacy and tolerance of incretinomimetics which showed these products to have modest efficacy (reduction in HbA1c levels of -0.74% compared to placebo for DPP-4 inhibitors and also showed them to be not inferior to active comparators)[11].
A statistically significant reduction in the HbA1c level was observed in oral bitherapy and oral tritherapy.
In bitherapy, this reduction of around -0.6% is very modest and much lower than that observed in the other studies carried out with sitagliptin versus active comparators.[12].
In tritherapy, this difference was greater than that observed in bitherapy, around -0.9%.
Moreover, sitagliptin was most effective up to the 12th week of treatment. After that point HbA1c levels increased slightly in the overall population and in each of the strata.

It would have been better if separate bitherapy and tritherapy studies versus validated therapeutic combinations had been available. However, the stratified analysis is methodologically acceptable.
Overall, the effect of sitagliptin is modest in terms of the reduction inHbA1c levels compared to existing alternatives.
It is unfortunate that a more robust analysis was not carried out on the endpoint "percentage of patients with an HbA1c level of <6.5% and <7%", which is clinically relevant as it relates to the therapeutic objectives.

- **In terms of tolerance,** in the overall study population, the adverse events which were observed more frequently in the sitagliptin group than in the placebo group were infections (generally cases of rhinopharyngitis and upper respiratory tract infections) and metabolic disorders (mainly hypoglycaemia).

A larger number of patients experienced attacks of hypoglycaemia in the sitagliptin group (27 patients, 55 attacks in total) than in the placebo group (4 patients, 20 attacks in total). More hypoglycaemic attacks were reported in stratum 2. No cases of severe hypoglycaemia were observed.[13]
The data obtained from analysis of the tolerance data of all the clinical studies available and in the latest PSUR did not show any new signals as to the tolerance of sitagliptin. However, a new warning relating to hypersensitivity reactions has been added to the SPC since this product was placed on the market.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

4.1.1. in oral bitherapy, in combination with a sulphonylurea:

Type 2 diabetes is a chronic disease with potentially serious complications.
JANUVIA is used in the context of treatment for hyperglycaemia.

10 Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. Renee E. Amori et al. JAMA 2007; 298 (2) : 194-206

11 The average changes in HbA1c levels observed were:
- -1 to -1.5% with metformin
- -1 to -1.5% with sulphonylureas
- -1% with glitazones
- -0.8% with glinides
- -0.5 to 1% with alphaglucosidase inhibitors

12 versus metformin: statistically significant reduction in HbA1c levels of -0.65%
Versus pioglitazone: statistically significant reduction of -0.70%

13 as a reminder, the number of hypoglycaemic attacks had been similar in the placebo and sitagliptin groups during studies in combination with metformin or pioglitazone (see the Committee's opinion on JANUVIA dated 6 June 2007)

The efficacy/adverse effects ratio of JANUVIA is moderate, given its very modest efficacy in reducing HbA1c levels.
The role of JANUVIA in oral bitherapy in combination with a sulphonylurea is limited. There are drug alternatives to this proprietary medicinal product.

Public health benefit:
The public health burden which type 2 diabetes represents is considerable. The burden represented by the sub-population of patients for whom JANUVIA is indicated (bitherapy) is moderate.
Improving the therapeutic management of type-2 diabetics is a public health need.
The data available does not allow assessment of the additional impact of JANUVIA on glycaemic control and on morbidity, mortality and quality of life compared to the bitherapies currently available.
The legitimacy of transposing the experimental data into clinical practice is doubtful because of various uncertainties, particularly relating to:
- the long-term effect of this treatment, including the effect on glycaemic control,
- the profile of patients in France, which may well be different from that of patients taking part in the trial (it was an international trial with only two sites in France).

The current state of understanding is such that it is impossible to reach any conclusions as to how JANUVIA might meet the identified public health need.
Consequently, JANUVIA is not expected to have an impact on public health in this extension of indication to bitherapy.

* part of the established priorities [priorities laid down by the National Technical Objective Definitions Group (DGS-2003)]

The actual benefit of JANUVIA is low.

4.1.2. in oral tritherapy, in combination with a sulphonylurea and metformin

Type 2 diabetes is a chronic disease with potentially serious complications.
JANUVIA is used in the context of treatment for hyperglycaemia.
The efficacy/adverse effects ratio of JANUVIA is high. The reduction in HbA1c levels is similar to that generally observed with other antidiabetics.
JANUVIA is an additional treatment option for the management of patients with type 2 diabetes. There are drug alternatives to this proprietary medicinal product.

Public health benefit:
The public health burden which type 2 diabetes represents is considerable. The burden represented by the sub-population of patients for whom JANUVIA is indicated (tritherapy) is moderate.
Improving the therapeutic management of type-2 diabetics is a public health need.
The data available does not allow assessment of the additional impact of JANUVIA on glycaemic control and on morbidity, mortality and quality of life compared to the tritherapies currently available.
The legitimacy of transposing the experimental data into clinical practice is doubtful because of various uncertainties, particularly relating to:
- the long-term effect of this treatment, including the effect on glycaemic control,
- the profile of patients in France, which may well be different from that of patients taking part in the trial (it was an international trial with only two sites in France).

The current state of understanding is such that it is impossible to reach any conclusions as to how JANUVIA might meet the identified public health need.
Consequently, JANUVIA is not expected to have an impact on public health in this extension of indication to tritherapy.

* part of the established priorities [priorities laid down by the National Technical Objective Definitions Group (DGS-2003)]

The actual benefit of JANUVIA is substantial.

4.2. Improvement in actual benefit (IAB)

JANUVIA does not provide any improvement in actual benefit (IAB V) in the management of patients with type 2 diabetes in oral bitherapy in combination with a sulphonylurea or in oral tritherapy in combination with metformin and a sulphonylurea.

4.3. Therapeutic use

The objectives of therapy are:

- Glycaemic control: control of HbA1c,
- Control of associated risk factors.

According to the guideline on 'Medical treatment of type 2 diabetes', published by AFSSAPS and HAS in November 2006, initial treatment for type 2 diabetes is based on the evaluation of and realistic changes to lifestyle (diet and exercise). Active steps to combat a sedentary lifestyle as well as dietary planning are essential measures at all stages in the management of this disease.
Oral antidiabetics are introduced when dietary and lifestyle measures (DLM) alone are not enough to control blood glucose levels: HbA1c > 6%. There are four classes of oral antiabetics: metformin, intestinal alpha-glucosidase inhibitors (AGIs), insulin secretagogues, and glitazone.

One of the following bitherapies may be offered at the oral bitherapy stage (when monotherapies have failed: HbA1c > 6.5% after six months of one of the monotherapies at the maximum dose):
- metformin + insulin secretagogue (sulphonylurea or glinide)
- metformin + glitazone
- metformin + intestinal alpha-glucosidase inhibitor
- insulin secretagogue + glitazone, for patients who are clearly and persistently intolerant of metformin or where metformin is contraindicated.
- or insulin secretagogue + alpha-glucosidase inhibitor (in the case of high post-prandial hyperglycaemia, but this combination is less effective in reducing HbA1c levels than the other combinations).

The combination must be selected in the light of the tolerance and contraindication profile of each class of drugs, the subject's age, the risk of hypoglycaemia, the level of hyperglycaemia, and each patient's individual clinical and biological profile (professional consensus).
These guidelines do not include three antidiabetic treatments which received marketing authorisation after 2006: exenatide, an incretin mimetic (marketing authorisation granted in November 2006), sitagliptin, a dipeptidyl peptidase-4 inhibitor (marketing authorisation granted in March 2007) and vildagliptin (marketing authorisation granted in September 2007).

The different treatment stages are summarised in the following table.
Treatment strategy (long-term condition 8 – Type 2 diabetes)[14]

HbA1c level	Treatment	Target HbA1c
HbA1c between 6% and 6.5% despite DLM	Monotherapy with metformin (or AGIs in the event of intolerance or contraindication)	< 6.5 %
HbA1c > 6.5 % despite DLM	Monotherapy with metformin or insulin secretagogue or AGI	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 secretagogue + glitazone or insulin + metformin ± other OAD except glitazone	Reduce HbA1c < 7%
HbA1c > 8 % despite tritherapy and DLM	Insulin + metformin ± other OAD except glitazone	Reduce HbA1c < 7%

DLM: diet and lifestyle measures; OADs: oral antidiabetics; IAG: intestinal alphaglucosidase inhibitor

Role of JANUVIA in oral bitherapy:
The bitherapy treatment alternatives available to patients for whom metformin is contraindicated or poorly tolerated are combinations of sulphonylurea + glitazone (a combination which can cause hypoglycaemia or weight gain) or sulphonylurea + IAG (a combination which causes digestive disorders).
The sulphonylurea + sitagliptin combination could offer a new alternative to patients unable to use these combinations because of adverse effects, but the quantitative effect in terms of reduction in HbA1c levels is very minor. This could be due to the mode of action of sulphonylurea and sitagliptin, both of which act on insulin secretion.
Consequently, the Committee stresses the limited role for the sulphonylurea + sitagliptin combination where metformin in combination with a sulphonylurea is contraindicated or not tolerated.

Role of JANUVIA in oral tritherapy:
In tritherapy, the alternative treatments are the combinations metformin + sulphonylurea + glitazone, metformin + sulphonylurea + exenatide, and insulin combined with other oral antidiabetics except glitazone.
In view of these alternatives, the tritherapy metformin + sulphonylurea + sitagliptin would be suitable for patients in whom glitazones are contraindicated or who put on weight when treated with a tritherapy including glitazone, as an alternative to exenatide or insulin.
As no direct comparisons with tritherapies are available, none can be particularly recommended.
This is an additional treatment option for the management of patients with type 2 diabetes, but JANUVIA must not be administered to patients with moderate to severe renal insufficiency.

4.4. Target population
According to the marketing authorisation indications, the target population for JANUVIA comprises type 2 diabetics being treated:
- by a sulphonylurea, where glycaemia is inadequately controlled despite the patient taking a maximum safe dose of sulphonylurea combined with diet and exercise and where metformin is not appropriate due to intolerance or a contraindication,
- by a sulphonylurea in combination with metformin where glycaemic control is inadequate despite the patient taking a maximum safe dose of these two drugs and following diet and exercise advice.

14 Management of diabetes: type 2 diabetes. Guide for physicians - Long-term condition, HAS - May 2006

The data from the study conducted on the basis of the Permanent sample of individuals covered by national insurance in France (EPAS), set up by the French National Health Insurance Scheme for Employees (CNAMTS)[15] indicates that the prevalence of diabetes undergoing treatment in mainland France (all types of insurance schemes) was 3.8% in 2005 and that the average annual increase observed between 2000 and 2005 was 5.7%. In the light of these percentages, and assuming that the average annual increase observed between 2000 and 2005 was repeated between 2005 and 2006 and between 2006 and 2007, the number of diabetic patients receiving treatment in 2007 would be around 2,485,000 patients[16].
Of those, 91% would be type 2 diabetics (ENTRED study, 2001-2003 – réseau diabète No 29 – September 2006).
According to the partially published results of the ECODIA 2 study (Réseaux diabète No 31 – March 2007), 83.2% of type 2 diabetics are treated with an oral antidiabetic without insulin; of these, 21.6% are treated with sulphonylurea monotherapy and 24.6% with metformin + sulphonylurea bitherapy.

Oral bitherapy:
- 83.2% of type 2 diabetics are treated by oral antidiabetics without insulin, and 21.6% of these are treated by sulphonylurea monotherapy,
- 68% of patients have an HbA1c level above 6.5%,
- the percentage of patients for whom metformin is contraindicated or not tolerated is unknown. It is assumed that this might apply to 20% of patients.

Consequently, the population of patients who fail properly conducted monotherapy with sulphonylurea and for whom metformin is not appropriate because of intolerance or contraindication would be 55,300 individuals.

Tritherapy:
- 83.2% of type 2 diabetics are treated by oral antidiabetics without insulin, and 24.6% of these are treated by metformin and sulphonylurea bitherapy,
- 51.5% of patients have an HbA1c level above 7%,

The population of patients who fail properly conducted metformin and sulphonylurea bitherapy would therefore amount to 238,400 individuals.

The Committee repeats that JANUVIA must not be administered to patients with moderate to severe renal insufficiency.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion of JANUVIA 100 mg on the list of medicines refundable by National health Insurance (boxes of 28 tablets) and on the list of medicines approved for hospital use and various public services (boxes of 28 and 50 tablets) in the indications and at the posology given in the marketing authorisation.

4.5.1 Packaging: Appropriate for the prescription conditions
4.5.2 Reimbursement rate:
65% in tritherapy in combination with a sulphonylurea and metformin.
35% in oral bitherapy in combination with a sulphonylurea

The transparency Committee requests that the follow-up study requested in 2007, the protocol for which is currently being validated, be extended to patients to whom these extensions of indications apply.

15 Diabète traité, quelles évolutions entre 2000 et 2005 [Treated diabetes, what changes between 2000 and 2005], Prat Organ Soins 2007; 38 (1):1-12
16 on the basis of the French population as recorded by the French National Statistics Office on 1 January 2008