HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

29 April 2009

VELMETIA 50 mg/850 mg, film-coated tablets
B/56 (CIP code: 386 778-0)

VELMETIA 50 mg/1 000 mg, film-coated tablets
B/56 (CIP code: 386 779-7)

Applicant: PIERRE FABRE MEDICAMENT

Sitagliptin/metformin

ATC code: A10BD07

List I

Date of Marketing Authorisation (centralised procedure): 16 July 2008

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

Medical, Economic, and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

sitagliptin / metformin

1.2. Indications

"For patients with type 2 diabetes mellitus, VELMETIA 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

- in combination with a sulfonylurea (i.e. triple combination therapy) in patients inadequately controlled on their maximal tolerated dose of metformin and a sulfonylurea."

1.3. Dosage

"The dose of antihyperglycaemic therapy with VELMETIA 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 on maximal tolerated dose of metformin monotherapy
For patients not adequately controlled on metformin alone, the usual starting dose of VELMETIA should provide **sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken**.

For patients switching from co-administration of sitagliptin and metformin
For patients switching from co-administration of sitagliptin and metformin in the form of separate tablets, VELMETIA should be initiated at the dose of sitagliptin and metformin already being taken.

For patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a sulfonylurea
The dose of VELMETIA 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 VELMETIA is used in combination with a sulfonylurea, a lower dose of the sulfonylurea may be required to reduce the risk of hypoglycaemia**.

For the different doses of metformin, VELMETIA is available in strengths of sitagliptin 50 mg and metformin hydrochloride 850 mg or 1000 mg.
All patients should continue their diet with an adequate distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.

VELMETIA should be given twice daily with meals to reduce the gastrointestinal undesirable effects associated with metformin.

Patients with renal insufficiency
VELMETIA should not be used in patients with moderate or severe renal impairment (creatinine clearance < 60 mL/min).

Patients with hepatic insufficiency
VELMETIA should not be used in patients with hepatic impairment.

Elderly
As metformin and sitagliptin are excreted by the kidney, VELMETIA 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. Limited tolerance data on sitagliptin is available in patients > 75 years of age and care should be exercised.

Paediatric population
VELMETIA is not recommended for use in children below 18 years of age due to a lack of data on its tolerance and efficacy in this population."[1]

1.4. Contraindications

- Hypersensitivity to the active substances or to any of the excipients
- Diabetic ketoacidosis, diabetic pre-coma
- **Moderate or severe renal impairment** (creatinine clearance < 60 mL/min)
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock, intravascular administration of iodinated contrast agents
- Acute or chronic disease which may cause tissue hypoxaemia, such as:
  - **cardiac or respiratory failure,**
  - **recent myocardial infarction**
  - shock.
- **Hepatic impairment**
- Acute alcohol intoxication, alcoholism
- Lactation

1.5. Special warnings and major precautions for use (see SPC)[2]

"Renal insufficiency:
Metformin and sitagliptin are known to be substantially excreted by the kidney. Metformin-related lactic acidosis increases with the degree of impairment of renal function, therefore, serum creatinine concentrations should be determined regularly:
- at least once a year in patients with normal renal function
- at least 2 to 4 times a year in patients with serum creatinine levels at or above the upper limit of normal and in elderly patients.
Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive or diuretic therapy or when starting treatment with a nonsteroidal anti-inflammatory drug (NSAID).

Hypoglycaemia
Patients receiving VELMETIA **in combination with a sulfonylurea may be at risk for hypoglycaemia. Therefore, a reduction in the dose of the sulfonylurea may be necessary.**
Insufficient data are available on the use of VELMETIA in combination with insulin.

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[1] usual dose of sitagliptin: "the dose of JANUVIA is 100 mg once daily. The dosage of metformin should be maintained, and JANUVIA administered concomitantly."
usual dose of metformin: "the usual starting dose when combined with other oral antidiabetic agents is one tablet of GLUCOPHAGE 500 mg or 850 mg 2 or 3 times daily given during or after meals.
After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements.
In patients taking a high dose of metformin (2-3 g/day), two GLUCOPHAGE 500 mg tablets may be replaced by one GLUCOPHAGE 1000 mg tablet.
The maximum recommended dose of metformin is 3 g/day. "

[2] The special warnings and precautions for use related to the use of the fixed combination of vildagliptin and metformin (EUCREAS), notably in patients with hepatic insufficiency or heart failure, do not appear in the SPC for the fixed combination of sitagliptin and metformin (VELMETIA).

Hypersensitivity reactions
Postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin have been reported. **These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin,** with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue VELMETIA, 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, excluding insulins
A10BD	:	Combinations of oral blood glucose lowering drugs
A10BD07	:	Meformin and sitagliptin

2.2. Medicines in the same therapeutic category

Comparator medicines

- Dipeptidyl peptidase-4 (DPP-4) inhibitors, gliptins:

JANUVIA/XELEVIA 100 mg, film-coated tablets (sitagliptin), indicated for patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.

GALVUS 50 mg, tablets (vildagliptin), indicated "in the treatment of type 2 diabetes mellitus as dual oral therapy in combination with:

- metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin,
- a sulfonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulfonylurea and for whom metformin is inappropriate due to contraindications or intolerance,
- a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate."

(This medicinal product has not yet been included on the list of medicines reimbursed by National Insurance and approved for hospital use, see Transparency Committee Opinion dated 10 December 2008)

- medicinal products containing metformin and generic versions of these:

GLUCOPHAGE 500 mg, 850 mg, 1 000 mg, tablets, indicated for the treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control in adults (as monotherapy or in combination with other oral anti-diabetic agents), in children from 10 years of age and adolescents (as monotherapy or in combination with insulin).

Fewer diabetes-related complications were observed in overweight adult type 2 diabetics treated with metformin as first-line therapy, after failure of dietary measures.

- fixed combinations of a gliptin and metformin:

EUCREAS 50 mg/850 mg, 50 mg/1 000 mg (vildagliptin and metformin) indicated in the treatment of type 2 diabetes mellitus patients:

- - who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone,

- - or who are already treated with the combination of vildagliptin and metformin as separate tablets."

It is an other fixed combination of a gliptin and metformin being assessed at the same time by the Transparency Committee

JANUMET 50 mg/850 mg*, 50 mg/1 000 mg (sitagliptin and metformin) 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 and in combination with a sulfonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulfonylurea.

Another fixed combination of metformin and a gliptin which is being assessed at the same time by the Transparency Committee

*This dosage strength has been classified as providing insufficient clinical benefit (see Transparency Committee Opinion dated 29 April 2009).

2.3. Medicines with a similar therapeutic aim

- as dual oral therapy: in combination with metformin, in patients with type 2 diabetes with insufficient glycaemic control despite maximal tolerated dose with oral metformin monotherapy:
  - Hypoglycaemic sulfonylureas
  - Glitazones
  - Alpha-glucosidase inhibitors
  - Glinide
  - Injectable incretin mimetic, exenatide (BYETTA)

- as oral triple combination therapy: in combination with metformin and a sulfonylurea in patients with type 2 diabetes with insufficient glycaemic control despite maximal tolerated dose of dual combination therapy with metformin and sulfonylurea:
  - glitazones
  - insulin
  - injectable incretin mimetic

3 ANALYSIS OF AVAILABLE DATA

The clinical development of the combination sitagliptin and metformin (VELMETIA) is based on:

- 2 pharmacodynamic studies
- 2 pharmacokinetic studies:
  - one study which demonstrated that a fixed combination of sitagliptin and metformin (50 mg/850 mg and 50 mg/1 000 mg) was bioequivalent to a free combination of each of the active ingredients at the same doses
  - one study to confirm that there were no pharmacokinetic interactions between the constituents of the fixed combination.

No clinical trials have been carried out specifically with the fixed combination.

The only clinical efficacy data provided by the company concern a free combination of sitagliptin and metformin (studies 020 and 024 already assessed by the Transparency Committee[3], study 036 not assessed by the Committee[4]), and a free combination of

[3] Opinion on JANUVIA dated 6 June 2007

[4] This study, submitted to the EMEA, was the subject of an application for Marketing Authorisation variation for JANUVIA (change to section 5.1. Pharmacodynamic properties).

sitagliptin + metformin + glimepiride (study 035, see Committee opinion relating to the application for an extension of indication for XELEVIA as triple oral therapy).

A summary of the Committee's conclusions on studies 020 and 024 assessed in June 2007 is given below:
"In the placebo-controlled trial 020 in combination with metformin, the reduction in HbA1c level (mean baseline HbA1c level 8%) after 24 weeks' treatment, was greater in the group of patients treated with the combination of sitagliptin and metformin than in the group treated with metformin alone, i.e. -0.67% versus -0.02% (difference between treatments = 0.65%, CI = 95% (-0.77,-0.53) p<0.001).
In trial 024 versus glipizide (sulfonylurea), after 52 weeks' treatment the combination sitagliptin and metformin was not inferior to the combination glipizide and metformin in reducing HbA1c level (-0.67% in both groups) in patients poorly controlled (mean baseline level = 7.5%) by metformin at a stable dose of ≥ 1500 g/day. However, the level of evidence for this non-inferiority trial is suboptimal, as glipizide was not used at maximum dose and treatment was discontinued due to lack of efficacy more frequently in the sitagliptin and metformin group than in the glipizide and metformin group.
- In terms of adverse effects, in combination with metformin, in the placebo-controlled trial 020 the most frequently reported adverse reactions in the sitagliptin group were nausea, upper abdominal pain, diarrhoea, falls in blood glucose level, and drowsiness.
The number of episodes of symptomatic hypoglycaemia was similar in the placebo and sitagliptin groups.
Moreover, in trial 024, the combination sitagliptin + metformin caused fewer episodes of symptomatic hypoglycaemia than the combination glipizide + metformin.
Changes in weight with sitagliptin were similar to those observed with placebo in trial 020. Conversely, in trial 024 weight loss was reported with the combination sitagliptin + metformin, while weight gain was recorded with the combination glipizide + metformin.
Under the European Risk Management Plan, infection, gastrointestinal disorders, rheumatic disorders and neuropsychiatric disorders require special monitoring.
- The combination sitagliptin + metformin was has only been evaluated by comparison with the combination sulfonylurea+ metformin. The Committee therefore has no other direct comparisons which would allow the benefits of the combination sitagliptin + metformin to be quantified in comparison with other dual therapies, particularly glitazone + metformin."

Results of study 036 (submitted to the EMEA and mentioned in the EPAR for VELMETIA, in the same way as the other trials carried out as part of the development process for JANUVIA):
This study was the subject of an application for variation of the Marketing Authorisation for JANUVIA (change to section 5.1. Pharmacodynamic properties).
The aim of the study was to demonstrate the superiority of free combinations of sitagliptin 50 mg twice daily + metformin 1 000 mg twice daily and sitagliptin 50 mg twice daily + metformin 500 mg twice daily compared with each of the active ingredients given as monotherapy.
This study will not be described in this document as it did not assess the fixed combination. NB this study did not assess a free combination of sitagliptin 50 mg twice daily + metformin 850 mg twice daily.

Results of trial 035: after 24 weeks' treatment with triple combination therapy, the reduction in HbA1c was greater in patients taking glimepiride + metformin + sitagliptin than in patients taking glimepiride + metformin + placebo (difference between sitagliptin and placebo = -0.89%, CI = 95% [-1.10 ; -0.68]; p<0.001).

The analysis of tolerance was performed on the following data:
- data from study 036 at 24 and 54 weeks,
- data from study 035 at 24 weeks (focusing on the global population and the population receiving triple combination therapy);

- analysis of the tolerance of dual combination therapy with sitagliptin + metformin, submitted to the EMEA's Committee for Medicinal Products for Human Use (CMPH), including the following five phase III clinical trials: 020 and 024 (submitted when the medicinal product was first included, with tolerance data updated after 2 years), 035 at 52 weeks, 036 updated at 54 weeks (1 year) and 053, data available at 30 weeks;
- updated pharmacovigilance data (PSUR).

A total of 1 685 patients have been exposed to the combination of sitagliptin + metformin in phase II and phase III trials carried out using the combination, in which 116 patients (trial 035) were treated with triple combination therapy with metformin + sulfonylurea + sitagliptin.
The only adverse effects anticipated for VELMETIA are those already known for sitagliptin with the available postmarketing experience, and for metformin, whose tolerance profile has been very thoroughly documented. The EMEA has not produced a specific Risk Management Plan for this new combination. However, a new warning about hypersensitivity reactions has been added to the SPC.

Only pharmacokinetic studies or studies evaluating a free combination have been submitted.
Despite the demonstration of bioequivalence between a fixed combination and each of the active ingredients used separately, there are no comparative clinical trials against the two active ingredients used separately and against other forms of dual combination therapy, which would make it possible to evaluate the efficacy and tolerance of this fixed combination.
It should be emphasised that a free combination of sitagliptin + metformin using a metformin dose of 850 mg twice daily has not been evaluated in any clinical trials.
There are therefore very few data available for this free combination of sitagliptin 50 mg and metformin 850 mg.

It is difficult to assess the benefits of the fixed combination compared with the two active ingredients used separately.

In addition, the fixed combination raises the problem of dose adjustment, particularly for one of the dosage strengths. A dose of metformin 850 mg twice daily is low compared with the doses evaluated in the available trials, notably the UKPDS trial, which evaluated the effects of metformin on morbidity and mortality, with a mean daily metformin dose of 2 550 mg a day (i.e. 850 mg 3 times a day).
The strengths of metformin used in fixed combinations restrict the possibility of adjusting the dose when necessary. This fixed combination will only be used in patients treated with a maximum dose of metformin 850 mg and 1 000 mg twice daily. The fixed combination is not relevant in patients treated with a maximum dose of e.g. 850 mg 3 times a day (which is often the case in normal practice).
It should be remembered that according to the guidelines, metformin should be used as monotherapy with the option of increasing doses up to 2 000 - 3 000 mg a day if blood glucose control is inadequate and if these doses are well tolerated, before adding another oral antidiabetic. The twice-daily dose of metformin 850 mg in a fixed combination is therefore not suitable for treating patients.
Only a combination of 50 mg/1 000 mg can be justified in clinical practice.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

VELMETIA 50 mg/850 mg, film-coated tablets

Type 2 diabetes is a chronic disease with potentially serious complications.
The medicinal product VELMETIA is used as a treatment for hyperglycaemia.
There is no evidence to show that a dose of metformin 850 mg twice daily has any clinical benefit. In this regard, the benefit for patients of a fixed combination of 50 mg + 850 mg has not been established. This dose is not suitable for clinical practice as few of the patients who have reached the stage of dual or triple combination therapy stage are being treated with metformin 850 mg twice daily.
The efficacy/adverse effects ratio has not been clearly established.
In the light of the available evidence, it is difficult to determine the role of VELMETIA in the treatment strategy. Alternative medicinal products exist.

Public health benefit

The public health burden of type 2 diabetes is substantial. The public health burden in the subpopulation of patients with an indication for VELMETIA (dual and triple combination therapy) is moderate.
Improving the management of type 2 diabetics is a public health need*.
However, this need is already partly covered by existing therapies (including a free combination of vildagliptin or sitagliptin and metformin).
There is no evidence to support any clinical benefit from this fixed combination compared with a free combination of the same two active ingredients. It is therefore not anticipated that VELMETIA will have any impact on morbidity and mortality or on quality of life.
Consequently it is not anticipated that VELMETIA will contribute any public health benefit in indications requiring dual or triple combination therapy.
***** an established priority [GTNDO priorities; GTNDO = French national rare diseases plan (DGS-2003)]

The Committee considers that the actual benefit provided by VELMETIA 50 mg/850 mg is insufficient for reimbursement by National Health Insurance compared with existing therapies.

VELMETIA 50 mg/1 000 mg, film-coated tablets

Type 2 diabetes is a chronic disease with potentially serious complications.
The medicinal product VELMETIA is used as a treatment for hyperglycaemia.
As with a free combination of sitagliptin + metformin, the efficacy/ adverse effects ratio is important both in dual combination therapy with sitagliptin + metformin and in triple combination therapy in combination with a sulfonylurea.
Alternative medicinal products exist.

Public health benefit

The public health burden of type 2 diabetes is substantial. The public health burden in the subpopulation of patients with an indication for VELMETIA (dual and triple combination therapy) is moderate.
Improving the management of type 2 diabetics is a public health need*.
However, this need is already partly covered by existing therapies (including a free combination of vildagliptin or sitagliptin and metformin).
There is no evidence to support any clinical benefit from this fixed combination compared with a free combination of the same two active ingredients. It is therefore not anticipated that VELMETIA will have any impact on morbidity and mortality or on quality of life.
Consequently it is not anticipated that VELMETIA will contribute any public health benefit in indications requiring dual or triple combination therapy.

***** an established priority [GTNDO priorities; GTNDO = French national rare diseases plan (DGS-2003)]

The actual benefit provided by VELMETIA, 50 mg/1 000 mg is substantial for all its indications.

4.2. Improvement in actual benefit (IAB)

VELMETIA 50 mg/850 mg, film-coated tablets
Not applicable

VELMETIA 50 mg/1 000 mg, film-coated tablets
VELMETIA 50 mg/1 000 mg, a fixed-dose combination containing sitagliptin 50 mg and metformin 1 000 mg, does not provide any improvement in actual benefit (IAB V) compared with the joint use of each of its ingredients taken separately.

4.3. Therapeutic use
The treatment objectives are:

- Glycaemic control: control of HbA_{1c},
- Control of associated risk factors.

According to the guideline 'Drug therapy in type 2 diabetes', published by AFSSAPS and HAS in November 2006, initial treatment for type 2 diabetes is based on evaluation and realistic modification of lifestyle (diet and exercise). A diet plan and active measures against a sedentary lifestyle are essential interventions at all stages of management of the disease.
Oral antidiabetics should be introduced when blood glucose is no longer adequately controlled (HbA_{1c} > 6%) by dietary and lifestyle measures (DLM). There are four categories of oral antidiabetics: metformin, intestinal alpha-glucosidase inhibitors (AGIs), insulin secretagogues, and glitazone.

At the dual oral combination therapy stage (failure of monotherapy: HbA_{1c} > 6.5% after 6 months of one form of monotherapy at maximum dose), one of the following dual combination therapies may be proposed:
- metformin + insulin secretagogue (sulfonylurea or glinide)
- metformin + glitazone
- metformin + alpha-glucosidase inhibitor
- insulin secretagogue + glitazone, in patients with confirmed and persistent inability to tolerate metformin, or contraindication to metformin.
- or insulin secretagogue + alpha-glucosidase inhibitors (in patients with high post-prandial hyperglycaemia, but lesser impact on HbA_{1c} than the other combinations).

When choosing a combination it is important to take into account the side effects of and contraindications to each category of drugs, the subject's age, risk of hypoglycaemia, degree of hyperglycaemia, and clinical and biochemical values for each individual patient (Agreement among professionals).
These guidelines do not include three antidiabetic therapies which obtained a Marketing Authorisation after 2006, namely exenatide, an incretin mimetic (Marketing Authorisation in November 2006), sitagliptin, a dipeptidyl peptidase-4 inhibitor (Marketing Authorisation in March 2007) and vildagliptin (Marketing Authorisation in September 2007).

The various stages of the treatment strategy are described in the table below.

Treatment strategy (Long-term condition 8 – Type 2 diabetes) [5]

Initial HbA_{1c}	**Treatment**	**Target HbA_{1c}**
HbA_{1c} between 6% and 6.5% despite DLM	Metformin monotherapy (or AGI in the event of intolerance or contraindication)	< 6.5 %
HbA_{1c} > 6.5 % despite DLM	Metformin monotherapy or insulin secretagogue or AGI	Maintain HbA_{1c} < 6.5%
HbA_{1c} > 6.5% despite monotherapy and DLM	Dual combination therapy	Maintain HbA_{1c} < 6.5%
HbA_{1c} > 7% despite dual combination therapy and DLM	- triple combination therapy: metformin + insulin secretagogue + glitazone or - insulin + metformin ± other OAD except glitazone	Reduce HbA_{1c} < 7%
HbA_{1c} > 8 % despite triple combination therapy and DLM	- insulin + metformin ± other OAD except glitazone	Reduce HbA_{1c} < 7%

DLM: diet and lifestyle measures; OAD: oral antidiabetics; AGI: alpha-glucosidase inhibitor

Role of VELMETIA, 50 mg/1 000 mg in the treatment strategy:

It should be remembered that:

- the guidelines "Drug therapy in type 2 diabetes" do not describe any role for sitagliptin (Marketing Authorisation March 2007);
- in the absence of any direct comparisons, the Committee has not been able to quantify the contribution of a free combination of sitagliptin + metformin compared with other forms of dual combination therapy (other than sulfonylurea + metformin).

VELMETIA 50 mg/1 000 mg should be used as an adjunct to diet and exercise in patients when blood glucose is inadequately controlled by the maximum tolerated dose of metformin monotherapy or in patients already treated with a free combination of sitagliptin + metformin at the same doses (replacement therapy).

The Committee has not been able to quantify the contribution of the free combination.

For triple combination therapy, the treatment options are the combinations sulfonylurea + glitazone + metformin, sulfonylurea + exenatide + metformin, and combinations of insulin with other oral antidiabetics (excluding glitazone).

In view of these options, triple combination therapy with sulfonylurea + sitagliptin + metformin should be used in patients with a contraindication to glitazones or who are gaining weight under triple combination therapy with glitazone, as an alternative to exenatide or insulin.

In the absence of direct comparisons with the available forms of triple combination therapy, none of these combinations can be recommended in preference to any other.

This is an adjuvant therapy for patients with type 2 diabetes.

4.4. Target population

According to the indication in the Marketing Authorisation, the target population for VELMETIA is patients with type 2 diabetes treated with:

- metformin when blood glucose is inadequately controlled by diet, exercise and metformin
- a sulfonylurea combined with metformin, when blood glucose is inadequately controlled despite a maximum tolerated dose of both these drugs, with diet and exercise.

Data from a study based on the permanent sample of French national insurance scheme members (*EPAS*) established by the National Salaried Workers' Health Insurance Fund (CNAMTS)[6] show that the prevalence of treated diabetes in metropolitan France taking all

[5] Management of type 2 diabetes Doctor's guide – Long-term condition (ALD), HAS – May 2006

[6] Diabète traité, quelles évolutions entre 2000 et 2005 [Treated diabetes, changes between 2000 and 2005], Prat Organ Soins 2007; 38 (1):1-12

regimens together was 3.8% in 2005, with a mean annual increase between 2000 and 2005 of 5.7%. Based on these percentages and on the hypothesis that the mean annual increase observed between 2000 and 2005 was the same between 2005 and 2006 and remained the same between 2006 and 2007, the number of diabetic patients treated in 2007 would be approximately 2 485 000 patients[7].
91% of those patients would be type 2 diabetics (ENTRED study, 2001-2003 – *Réseaux Diabète* No 29 – September 2006).
According to the results of the ECODIA 2 study, published in part (*Réseaux diabète* No.31 – March 2007), 83.2% of type 2 diabetics are being treated with an oral antidiabetic without insulin, with 24% of them treated with metformin monotherapy and 24.6% treated with sulfonylurea + metformin dual combination therapy.

Dual oral combination therapy:
- 83.2% of type 2 diabetics are treated with an oral antidiabetic without insulin, 24% of whom are treated with metformin monotherapy,
- 68% of patients have an HbA_{1c} value > 6.5%,

The population of patients who have failed properly-conducted metformin monotherapy is therefore 307 000.

Triple oral combination therapy:
- 83.2% of type 2 diabetics are treated with an oral antidiabetic without insulin, 24.6% of whom are treated with sulfonylurea + metformin,
- 51.5% of patients have an HbA_{1c} value > 7%.

Based on these figures, the population of patients who have failed properly-conducted dual oral combination therapy with metformin and sulfonylurea is 238 400.

The Committee notes that VELMETIA should not be used in patients with moderate to severe renal failure or with heart failure or liver failure.
The population figures given above are therefore a maximum estimate of the population described in the Marketing Authorisation.

4.5. Transparency Committee recommendations

VELMETIA 50 mg/850 mg, film-coated tablets
The Transparency Committee does not recommend inclusion on the list of medicines reimbursed by National Health Insurance nor on the list of medicines approved for use by hospitals and various public services.

VELMETIA 50 mg/1 000 mg, film-coated tablets
The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for use by hospitals and various public services in the indications and at the dosage given in the Marketing Authorisation.

Packaging (B/56 and B/50): not appropriate for the prescription conditions; packaging in boxes of 60 and 180 tablets would be preferable

Reimbursement rate: 65%

[7] Based on the INSEE (National Institute for Statistics and Economic Studies) French population at 01 January 2008