HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

29 April 2009

EUCREAS 50 mg/850 mg, tablet
Box of 60 (CIP: 382 765-1)
Box of 180 (CIP: 571 759-9)

EUCREAS 50 mg/1000 mg, tablet
Box of 60 (CIP: 382 770-5)
Box of 180 (CIP: 571 766-5)

Applicant: NOVARTIS PHARMA SAS

vildagliptin/metformin

ATC code: A10BD08

List I

Date of Marketing Authorisation (centralised procedure): 14 November 2007, modified on 13 February 2008

Reason for request: Inclusion on the list of medicines reimbursed by National Health Insurance (box of 60) and approved for use by hospitals (boxes of 60 and 180).

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

vildagliptin/metformin

1.2. Indications

"EUCREAS is indicated in the treatment of type 2 diabetes mellitus:
- in patients who are unable to achieve adequate 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."

1.3. Dosage

"Adults
Based on the patient's current dose of metformin, EUCREAS may be initiated at either the 50 mg/850 mg or 50 mg/1000 mg tablet strength twice daily, one tablet in the morning and the other in the evening. The recommended daily dose is 100 mg vildagliptin plus 2000 mg metformin hydrochloride.
Patients receiving vildagliptin and metformin from separate tablets may be switched to EUCREAS containing the same doses of each component.
Doses higher than 100 mg of vildagliptin are not recommended.
There is no clinical experience of vildagliptin and metformin in triple combination with other antidiabetic agents.
Taking EUCREAS with or just after food may reduce gastrointestinal symptoms associated with metformin.

Additional information on special populations
Renal impairment
EUCREAS should not be used in patients with creatinine clearance < 60 ml/min.
Hepatic impairment
EUCREAS should not be used in patients with hepatic impairment, including those with pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times the upper limit of normal (ULN).
Elderly (≥ 65 years)
As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking EUCREAS should have their renal function monitored regularly. EUCREAS has not been studied in patients older than 75 years. Therefore the use of EUCREAS is not recommended in this population.
Children and adolescents (< 18 years)
EUCREAS is not recommended for use in children and adolescents due to a lack of data on tolerance and efficacy."[1]

[1] Usual dosage of vildagliptin: "in combination with metformin, the recommended daily dose of vildagliptin is 100 mg, given as a 50 mg dose in the morning and a 50 mg dose in the evening.
Usual dosage of metformin: in combination with other oral antidiabetics, the usual initial dosage is one tablet of GLUCOPHAGE 500 mg or 850 mg two to three times daily, given with or after food.
After 10 to 15 days the dosage may be modified in accordance with blood glucose levels.
In patients taking a higher dose of metformin (2 to 3 g/day), it is possible to replace two tablets of GLUCOPHAGE 500 mg with one tablet of GLUCOPHAGE 1000 mg.
The maximum recommended dose of metformin is 3 g per day."

1.4. Contraindications

- Hypersensitivity to the active ingredients or to one of the excipients
- Diabetic ketoacidosis or diabetic precoma
- Renal impairment or alteration in renal function defined as a creatinine clearance < 60 ml/min.
- Acute conditions likely to impair renal function, such as: dehydration, serious infection, shock, intravascular administration of iodine-containing contrast media
- Acute or chronic conditions that can cause tissue hypoxia, such as:
    - heart failure or respiratory failure,
    - recent myocardial infarct,
    - shock.
- Hepatic impairment
- Acute intoxication with alcohol, alcoholism
- Breastfeeding

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

"Lactic acidosis

Lactic acidosis is a very rare but serious metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. In patients with impaired liver function, lactate clearance may be restricted. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors, such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any conditions associated with hypoxia.

Renal impairment

As metformin is excreted by the kidney, serum creatinine concentrations should be monitored regularly:

- at least once a year in patients with normal renal function
- at least two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly patients.

Renal impairment 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 an NSAID.

Hepatic impairment

Patients with hepatic impairment, including those with pre-treatment ALT or AST > 3x ULN, should not be treated with EUCREAS.

Liver enzyme monitoring

Rare cases of hepatic dysfunction (including hepatitis) have been reported with vildagliptin. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function tests (LFTs) returned to normal after discontinuation of treatment. LFTs should be performed prior to the initiation of treatment with EUCREAS in order to know the patient's baseline value. Liver function should be monitored during treatment with EUCREAS at three-month intervals during the first year and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent LFTs until the abnormality(ies) return(s) to normal. Should an increase in AST or in ALT of 3x ULN or greater persist, withdrawal of EUCREAS therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue EUCREAS.

Following withdrawal of treatment with EUCREAS and LFT normalisation, treatment with EUCREAS should not be re-initiated.

[2] The special warnings and precautions for use relating to hepatic impairment or heart failure are not given in the SPC of sitagliptin (JANUVIA).

Cardiac failure

Experience with vildagliptin therapy in patients with congestive heart failure of New York Heart Association (NYHA) functional class I-II is limited and therefore vildagliptin should be used cautiously in these patients. There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class III-IV and therefore use is not recommended in these patients.

Metformin is contraindicated in patients with heart failure, therefore EUCREAS is contraindicated in this patient population.

Skin disorders

Although skin lesions were not observed at an increased incidence in clinical trials, there was limited experience in patients with diabetic skin complications. Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering or ulceration, is recommended."

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
A10BD: Combinations of oral blood glucose lowering drugs
A10BD08: vildagliptin/metformin

2.2. Medicines in the same therapeutic category

Comparator medicines:

- Inhibitors of dipeptidyl peptidase-4 (DPP-4)/gliptins:

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

- metformin, in patients unable to achieve adequate glycaemic control even at the maximum tolerated dose of metformin on its own,
- a hypoglycaemic sulphonylurea, in patients unable to achieve adequate glycaemic control even at the maximum tolerated dose of the hypoglycaemic sulphonylurea, in whom metformin is unsuitable for reasons of tolerability or a contraindication,
- a thiazolidinedione, in patients unable to achieve adequate glycaemic control for whom use of a thiazolidinedione is appropriate."

(product not yet included on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals: see Committee Opinion of 10 December 2008)

JANUVIA/XELEVIA 100 mg film-coated tablets (sitagliptin), indicated in type 2 diabetics to improve glycaemic control, in combination with metformin, when diet, exercise and metformin do not achieve adequate glycaemic control.

- Metformin-based products and their generics:

GLUCOPHAGE 500 mg, 850 mg, 1000 mg tablets, indicated in the treatment of type 2 diabetes, particularly in patients who are overweight, when diet and exercise are insufficient to restore glycaemic control in adults (as monotherapy or in combination with other oral antidiabetics), children over 10 years and adolescents (as monotherapy or in combination with insulin).

A reduction in diabetes complications was observed in overweight adult type 2 diabetics treated with metformin hydrochloride as first-line treatment after failure of dietary measures.

- Gliptin/metformin fixed combinations:

JANUMET/VELMETIA 50 mg/850 mg*, 50 mg/1000 mg (sitagliptin/metformin), indicated in type 2 diabetics to improve glycaemic control alongside dietary measures and exercise in patients inadequately controlled by metformin alone at the maximum tolerated dose or in patients already treated with the sitagliptin/metformin combination.

Other gliptin/metformin fixed combination evaluated in parallel by the Transparency Committee

*This dosage achieved an inadequate ACB (see Transparency Committee Opinion of 29 April 2009).

2.3. Medicines with a similar therapeutic aim

Oral antidiabetic medicinal products that can be given alongside metformin in dual antidiabetic therapy indicated:

in type 2 diabetics who have not achieved adequate glycaemic control at the maximum tolerated doses of oral treatment based on metformin monotherapy:

- Hypoglycaemic sulphonylureas
- Glitazones
- Intestinal alpha-glucosidase inhibitors
- Glinides
- Injectable incretin mimetic: exenatide (BYETTA)

3 ANALYSIS OF AVAILABLE DATA

The clinical development of the vildagliptin/metformin fixed combination (EUCREAS) is based on three pharmacokinetics studies:

- two studies that demonstrated the bioequivalence of the vildagliptin + metformin fixed combination (50 mg/850 mg and 50 mg/1000 mg) with the free combination of each active ingredient at the same doses.
- a study that evaluated the influence of food on the pharmacokinetic parameters of the fixed combination.

The main clinical efficacy data supplied by the company are those relating to the vildagliptin-metformin free combination. These data have already been evaluated by the Transparency Committee[3].

The conclusions of these studies are summarised below:

- "As regards efficacy, the effect of vildagliptin (at doses of 1×50 mg/day or 2×50 mg/day) on the reduction in HbA1c was evaluated after 24 weeks of treatment in combination with metformin in type 2 diabetics inadequately controlled by metformin ≥ 1500 mg/day (studies 2303 and 2354). Noteworthy exclusion criteria included signs of renal impairment, liver disorders or a history of heart problems.

[3] Opinion on GALVUS of 10 December 2008

In combination with metformin, addition of vildagliptin 2 × 50 mg/day lowered HbA1c relative to continuation of treatment with metformin alone (difference between vildagliptin 2 × 50 mg/day and placebo: -1.10%, 95% CI [-1.37; -0.84]; p < 0.001, mean baseline level 8.4%).

In study 2354 versus an active comparator (pioglitazone at the non-optimal dose of 30 mg/day), in combination with metformin, addition of vildagliptin 2 × 50 mg/day was not inferior to that of pioglitazone on the reduction in HbA1c (-0.88% versus -0.98%, difference between treatments -0.10%, 95% CI [-0.05, -0.26], mean baseline level 8.4%).

In study 2308IA, the primary objective was to demonstrate the efficacy and long-term tolerance of the combination metformin + vildagliptin compared with the combination metformin + glimepiride in type 2 diabetics inadequately controlled by treatment with metformin alone (HbA1c > 6.5% and ≤ 8.5%) over a treatment period of up to 5 years. The protocol for this study specified an interim analysis after 1 year, the objective of which was to demonstrate the non-inferiority of the combination metformin + vildagliptin compared with the combination metformin + glimepiride in 2789 patients (1396 in the metformin + vildagliptin group, 1393 in the metformin + glimepiride group) in terms of the reduction in HbA1c.
The upper limit of the 97.5% confidence interval was below the set threshold. The combination metformin + vildagliptin was found to be non-inferior to the combination metformin + glimepiride.
Nevertheless, it is important to stress that a statistically significant difference in favour of the combination metformin + glimepiride was observed in terms of the achievement of the therapeutic objective (HbA1c < 6.5%) compared with the combination metformin + vildagliptin.
No difference was observed between the two treatment groups in terms of mean variation in fasting blood glucose.
The information provided by this interim analysis after 1 year was non-optimal in terms of expected definitive results.
In four out of five studies, the reduction in HbA1c was of a magnitude of -0.7%. This degree of efficacy was likewise observed by the authors of a meta-analysis4 of 29 studies that evaluated the efficacy and tolerance of incretin mimetics, who concluded that these products show modest efficacy (reduction in HbA1c relative to placebo of -0.74% for DPP-4 inhibitors, non-inferiority compared with the active comparators)5.

As regards to tolerance, in combination with metformin, versus placebo, the adverse effects most often seen in the vildagliptin group were nervous system (tremor, headache, dizziness) and gastrointestinal disorders (nausea). The number of hypoglycaemic episodes seen was similar in the placebo and vildagliptin groups. There was no change in body weight relative to baseline in patients taking vildagliptin 50 mg twice daily (+0.2 kg under vildagliptin, -1.0 kg under placebo).

In study 2354, body weight remained stable under metformin/vildagliptin, whereas weight gain was observed with the metformin/pioglitazone combination. A higher incidence of peripheral oedema was reported in the vildagliptin group than in the pioglitazone group.
In study 2308IA, the number of patients experiencing hypoglycaemic attacks was greater in the metformin + glimepiride group (224/1383) than in the metformin + vildagliptin group (23/1389). No severe hypoglycaemic attacks were observed in the metformin + vildagliptin

[4] 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
[5] The observed mean variation in HbA1c are of the order of:
- -1 to -1.5% with metformin
- -1 to -1.5% with sulphonylureas
- -1% with glitazones
- -0.8% with glinides
- -0.5 to 1% with alpha-glucosidase inhibitors

group, whereas 10 severe hypoglycaemic episodes were seen in the metformin + glimepiride group.
It should be stressed that the patients included had low HbA1c levels and that the titration of glimepiride seemed strict, which could have been responsible for a higher incidence of hypoglycaemia in the metformin + glimepiride group. After one year of treatment, the body weight had decreased by 0.23 kg in the metformin + vildagliptin group and increased by 1.56 kg in the metformin + glimepiride group (i.e. a difference of -1.79 kg, 95% CI [-2.10; -1.48], $p < 0.001$).

An updated analysis of the safety data, based on the combined data from controlled clinical studies as monotherapy and in combination regimens, involving some 7000 patients treated with GALVUS, did not show any increase in the risk of cardiovascular or cutaneous adverse events, angioedema or infections compared with placebo and comparator groups. The cumulative data from PSURs did not identify any new case of treatment-related liver disorders, new sign specific to the risk of serious infection, or an increased risk of angioedema. Nevertheless, concerns about the tolerance profile of GALVUS persist.

The European risk management plan includes, in particular, closer monitoring of skin disorders (with or without oedema or vascular disorders), liver disorders (including transaminases), angioedema, severe infections, cardiac conduction disturbances, and of patients with moderate to severe renal impairment or impaired heart function.

No study has demonstrated the superior efficacy of vildagliptin in combination with an oral antidiabetic over a comparator oral antidiabetic combination."

The company has also supplied the publication of a randomised double-blind study[6] over a period of 24 weeks that compared the vildagliptin + metformin fixed combination at dosages of 50 mg/1000 mg and 50 mg/500 mg with the separate administration of each of the active ingredients as monotherapy in 1179 type 2 diabetics naïve to all treatment and with a HbA1c level of between 7.5 and 11%.
Patients were defined as naïve to all treatment either if they had never undergone treatment with oral antidiabetics or if they had not been treated for twelve weeks prior to screening for a period not exceeding three months.
Patients were randomised either to the vildagliptin + metformin 50/1000 mg fixed combination (twice daily), the vildagliptin + metformin 50/500 mg fixed combination (twice daily), vildagliptin alone (50 mg twice daily), or metformin alone (1000 mg twice daily).
Only the efficacy results for the 50/1000 mg fixed combination are presented, because the marketing authorisation was granted for this dosage. The 50 mg/500 mg dosage was judged to be too weak by the registration authorities.
The characteristics of the patients included were as follows: mean age 53 years, mean duration of diabetes 24 months, BMI 31.3 kg/m²; HbA1c 8.7%.
The reduction in HbA1c relative to baseline was -1.8% for the vildagliptin + metformin fixed combination (50 mg/1000 mg). This fixed combination was superior to each of the active ingredients taken separately (the differences in terms of the reduction in HbA1c are not available, only the "p" values are reported).

The bioequivalence between the fixed combination and the separate administration of each active ingredient has been established. There is one study, published electronically, that has not been evaluated by the market authorisation authorities, in which the 50/1000 mg fixed combination was compared with the two active ingredients taken separately. There is no comparative clinical study versus other dual therapies that allow the evaluation of the efficacy and tolerance of this fixed combination. It should be stressed that there is no clinical study

[6] E. Bosi, F Dotta, Y Jia, M Goodman. Vildagliptin plus metformin combination therapy provides superior glycaemic control to individual monotherapy in treatment-naive patients with type 2 diabetes mellitus. Published online: Mar 23 2009

that evaluated the vildagliptin + metformin free combination at a metformin dose of 850 mg twice daily.
The available data on this free combination of 50 mg vildagliptin plus 850 mg metformin are thus very limited.

It is difficult to make any comparison between this fixed combination and the separate administration of the two active ingredients.

Moreover, it is not possible to adjust the dosage of just one of the active ingredients with this fixed combination. The metformin dosage of 850 mg twice daily is low by comparison with the doses evaluated in the available studies. This is particularly true in the UKPDS study that evaluated the effect of metformin in terms of morbidity/mortality; the mean daily dose of metformin was of 2550 mg/day (i.e. 850 mg three times daily).
The metformin doses in the fixed combination are a constraint on therapeutic adjustments. This fixed combination must be restricted to patients treated with a maximum metformin dosage of 850 mg and 1000 mg twice daily. For a patient treated with a maximum dosage of e.g. 850 mg three times daily (as is often the case in practice), this fixed combination is not appropriate.
It should be remembered that the guidelines state that patients on metformin should remain on monotherapy, with the option of increasing the daily dose to 2000-3000 mg if they are unable to achieve adequate glycaemic control and show good tolerability, before adding any other oral antidiabetic to the treatment regimen. The dosage of 850 mg metformin twice daily in the fixed combination is therefore unsuitable for the management of diabetic patients.
Only the 50 mg/1000 mg combination is justified in clinical practice.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

EUCREAS 50 mg/850 mg, film-coated tablet
Type 2 diabetes is a chronic disease with potentially serious complications.
The medicinal product EUCREAS is used in the treatment of hyperglycaemia.
The clinical benefit of a metformin dosage of 850 mg twice daily is unproven. At this dosage, the therapeutic benefit for patients of the 50 mg/850 mg fixed combination has not been established. This dosage is unsuitable for clinical practice, because few patients are treated at the dual or triple therapy stage at a metformin dosage of 850 mg twice daily.
The efficacy/adverse effects ratio is poorly established.
The therapeutic use is difficult to establish on the basis of the available information. Alternative medicinal products exist.

Public health benefit:
The public health burden of type 2 diabetes is considerable. The benefit for the subpopulation of patients corresponding to the indication for the medicinal product EUCREAS (dual therapy) is moderate.
Improving the therapeutic management of type 2 diabetics is a public health need*. However, existing treatments (including the free combination of vildagliptin/sitagliptin and metformin) are already helping to meet this need.
There is no evidence that this fixed-dose combination has any added benefit over a free combination of these two active ingredients. The medicinal product EUCREAS is not therefore expected to have any impact on morbidity/mortality and quality of life.
Consequently, EUCREAS is not expected to benefit public health as dual therapy in this indication.

*defined as a health priority by GTNDO: *Groupe Technique National de Définition des Objectifs [National technical group for the setting of public-health objectives] (DGS [Ministry of Health]-2003)

The Committee considers that the actual benefit of EUCREAS 50 mg/850 mg compared with existing therapies is insufficient for it to be covered by National Health Insurance.

EUCREAS 50 mg/1000 mg, film-coated tablet

Type 2 diabetes is a chronic disease with potentially serious complications.
The medicinal product EUCREAS is used in the treatment of hyperglycaemia.
As is the case for the vildagliptin + metformin free combination, the efficacy/adverse effects ratio is moderate when concerns about the tolerance profile of vildagliptin (particularly in terms of cardiovascular risk, skin lesions and liver disorders) are taken into account.
Alternative medicinal products exist.

Public health benefit:

The public health burden of type 2 diabetes is considerable. The benefit for the subpopulation of patients corresponding to the indication for the medicinal product EUCREAS (dual therapy) is moderate.
Improving the therapeutic management of type 2 diabetics is a public health need*. However, existing treatments (including the free combination of vildagliptin/sitagliptin and metformin) are already helping to meet this need.
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Consequently, EUCREAS is not expected to benefit public health as dual therapy in this indication.

*defined as a health priority by GTNDO: *Groupe Technique National de Définition des Objectifs [National technical group for the setting of public-health objectives] (DGS [Ministry of Health]-2003)

The actual benefit of the medicinal product EUCREAS 50 mg/1000 mg is substantial.

4.2. Improvement in actual benefit (IAB)

EUCREAS 50 mg/850 mg, film-coated tablet

None.

EUCREAS 50 mg/1000 mg, film-coated tablet

The medicinal product EUCREAS 50 mg/1000 mg, combining fixed doses of 50 mg of vildagliptin and 1000 mg of metformin, does not offer an improvement in actual benefit (IAB V) compared with the combined use of each of its constituents taken separately.

4.3. Therapeutic use

The objectives of therapy are:

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

According to the guideline “Medical treatment of type 2 diabetes’” published by AFSSAPS [French Health Product Safety Agency] and HAS in November 2006, initial treatment of 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.
The practitioner may resort to using oral antidiabetics when dietary and lifestyle measures (DLM) alone are not enough to control blood glucose levels: HbA1c > 6%. There are four classes: metformin, intestinal alpha-glucosidase inhibitors (AGIs), insulin secretagogues, and glitazone.

At the oral dual therapy stage (failure of monotherapy: HbA1c > 6.5% after 6 months of monotherapy at the maximum dose), one of the following dual therapies may be proposed:
- metformin + insulin secretagogue (sulphonylurea or glinide)
- metformin + glitazone
- metformin + alpha-glucosidase inhibitor
- insulin secretagogue + glitazone, in the event of persistent, confirmed intolerance to metformin or if metformin is contraindicated.
- or insulin secretagogue + alpha-glucosidase inhibitors (if post-prandial hyperglycaemia is substantial, but with lower efficacy on HbA1c 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 the individual patient's 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)[7]

HbA1c level	Treatment	Target HbA1c
HbA1c between 6% and 6.5% despite DLM	Monotherapy with metformin (or AGI 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	Dual therapy	Reduce HbA1c < 6.5%
HbA1c > 7% despite dual therapy and DLM	Triple therapy: metformin + insulin secretagogue + glitazone or insulin + metformin ± other OAD except glitazone	Reduce HbA1c < 7%
HbA1c > 8% despite dual therapy and DLM	Insulin + metformin ± other OAD except glitazone	Reduce HbA1c < 7%

DLM: Diet and lifestyle measures; OADs: oral antidiabetics; AGIs: intestinal alpha-glucosidase inhibitors

<u>Therapeutic use of EUCREAS:</u>

It should be noted that:
- the guidelines "Drug treatment of type 2 diabetes" do not define the use of vildagliptin (marketing authorisation granted in September 2007);
- the Committee was unable to quantify the advantage of a metformin + vildagliptin free combination versus other dual therapies (except metformin + sulphonylurea), as no direct comparisons were available.

EUCREAS 50 mg/1000 mg must be used as an adjunct to diet and exercise in patients whose glycaemia is inadequately controlled by metformin alone at the maximum tolerated dose or in patients who are already being treated by a vildagliptin/metformin free combination at the same doses (replacement treatment).

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

4.4. Target population

According to the indication defined in the marketing authorisation, the EUCREAS target population is type 2 diabetics treated with metformin who are unable to achieve adequate glycaemic control through diet, exercise and metformin.

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)[8] indicate that the prevalence of diabetes undergoing treatment in all types of insurance schemes was 3.8% in 2005 and that the average annual increase observed between 2000 and 2005 was 5.7%. Based on 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[9].
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, 24% are treated with metformin monotherapy.
The ECODIA-2 data indicate that 68% of patients have an HbA1c level above 6.5%.
The population of patients in whom properly conducted metformin monotherapy has failed would therefore amount to 307,000 individuals.

The Committee points out that the use of EUCREAS in patients with renal impairment, heart failure or hepatic impairment is not recommended.
These conditions constitute contraindications of metformin, but the exact number of patients concerned is difficult to calculate.
Consequently, the population figures given above are an upper-end estimate of the population corresponding to the marketing authorisation.

4.5. Transparency Committee recommendations

EUCREAS 50 mg/850 mg, film-coated tablet
The Transparency Committee does not recommend 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.

EUCREAS 50 mg/1000 mg, film-coated tablet
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 dosages specified in the marketing authorisation.

Packaging: appropriate for the prescription conditions

Reimbursement rate: 65%

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