HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
29 October 2014

EUCREAS 50 mg/1000 mg, film-coated tablet
B/60 (CIP: 34009 382 770 5 0)
B/3 x 60 (CIP: 34009 571 766 5 5)
EUCREAS 50 mg/1000 mg, film-coated thermoformed tablet
Boîte de 60 (CIP : 34009 273 490 1-0)
Boîte de 180 (3x60) (CIP : 34009 584 849 1-9)
ICANDRA 50 mg/1000 mg, film-coated tablet
B/60 (CIP: 34009 498 617 9 8)
B/3 x 60 (CIP: 34009 578 915 6 5)

Applicant: NOVARTIS PHARMA S.A.S.

INN	Vildagliptin/metformin
ATC code (2013)	A10BD08 (Combinations of oral blood glucose lowering drugs)
Reason for the review	**Extension of indication**
Lists concerned	B/60: **National Health Insurance** (French Social Security Code L.162-17) B/60 and B/180: **Hospital use** (French Public Health Code L.5123-2)
Indications concerned	**"EUCREAS/ICANDRA is indicated in triple combination therapy with insulin as an adjunct to diet and exercise to improve glycaemic control in adult patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control"**

Actual Benefit	**Moderate**
Improvement in Actual Benefit	**As there are no direct comparisons with validated and available triple therapies, and as there is no clinical study with the fixed-dose combination, the Transparency Committee considers that EUCREAS/ICANDRA does not provide any improvement in actual benefit (level V, non-existent) in the treatment of patients with type 2 diabetes in triple therapy, in combination with insulin.**
Therapeutic use	**Vildagliptin is a treatment option that can be added to the combination of insulin + metformin as triple therapy in patients who do not achieve or maintain glycaemic targets with a combination of insulin/metformin.** **The fixed-dose combination is reserved only for patients treated with a maximum dosage of 1000 mg of metformin administered twice per day. The dose of metformin in the fixed-dose combination limits therapeutic adjustments.** **This therapeutic situation (triple therapy with gliptin in combination with insulin and metformin) is for patients who cannot be treated with a sulfonylurea.**
Recommendations	**-**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (Centralised procedure)	Start date (EUCREAS): November 14th 2007 Start date (ICANDRA): December 1st 2008 Extension of indication (EUCREAS): October 25th 2012 Extension of indication (ICANDRA): October 29th 2012 Risk management plan + national monitoring
Prescribing and dispensing conditions/special status	List I

ATC Classification	2013	
	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

02 BACKGROUND

The EUCREAS/ICANDRA proprietary medicinal products are included on the list of medicines refundable by National Health Insurance and on the list of medicines approved for use by hospitals and various public services for the treatment of type 2 diabetes in adult patients whose glycaemic control is inadequate at their maximum tolerated dose of metformin in oral monotherapy, or in patients already treated with the combination of vildagliptin and metformin as separate tablets.[1]
EUCREAS is a fixed-dose combination of metformin and vildagliptin, which amplifies the incretin effect on the islets of Langerhans through a potent and selective inhibitory effect on dipeptidyl peptidase (DPP-4). EUCREAS should not be used in patients whose creatinine clearance is < 60 ml/minute.
This application concerns the use of EUCREAS **as an add-on to insulin,** when a stable dose of insulin and metformin in combination with diet and exercise do not provide adequate glycaemic control. The extension of indication in combination with a sulfonylurea (oral triple therapy) is the subject of a separate opinion.

By letter dated 2 July 2013, the Transparency Committee informed all companies using incretins (gliptins and GLP-1 analogues) of its desire to re-assess the actual benefit, the improvement in actual benefit, and the target population of all the proprietary medicinal products involved, due to signals of pancreatic damage potentially related to these medicines. In this context, the Committee suspended the assessment of all pending dossiers, including the EUCREAS/ICANDRA dossier.
The Committee office, at its meeting on March 12th 2014, decided not to perform the re-assessment of incretins. In the current state of knowledge and data available in the literature considered by the FDA, EMA and ANSM [French National Agency for Medicines and Health Products Safety], no evidence to date supports a link between incretins and increased risk of pancreatitis and pancreatic cancer which nevertheless remain risks to monitor.[2] These risks will be subject to enhanced pharmacovigilance monitoring in clinical studies of morbidity and mortality, and in epidemiological studies to which the Committee will remain attentive.

[1] Committee Opinion of 29 April 2009: Substantial Actual Benefit – IAB V.
[2] Egan AG et al. Pancreatic safety of incretin-based drugs-FDA and EMA assessment. N Engl J Med 2014; 370; 9.

03 THERAPEUTIC INDICATIONS

“EUCREAS/ICANDRA is indicated in the treatment of type 2 diabetes mellitus:

- EUCREAS/ICANDRA is indicated in the treatment of adult 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.[1]

- EUCREAS/ICANDRA is indicated in combination with a sulfonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled with metformin and a sulfonylurea.[3]

- **EUCREAS/ICANDRA is indicated in triple combination therapy with insulin as an adjunct to diet and exercise to improve glycaemic control in adult patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control."**

04 DOSAGE

“Adults
The dose of antihyperglycaemic therapy with EUCREAS/ICANDRA 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 vildagliptin. EUCREAS/ICANDRA 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.
…

For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin:
The dose of EUCREAS/ICANDRA should provide vildagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. …

Special populations
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.

Renal impairment
EUCREAS/ICANDRA should not be used in patients with creatinine clearance < 60 ml/min.

Hepatic impairment
EUCREAS/ICANDRA 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).

Paediatric population
EUCREAS/ICANDRA is not recommended for use in children and adolescents (< 18 years). The safety and efficacy of Eucreas in children and adolescents (< 18 years) have not been established. No data are available."

[1] Indication is the subject of a separate opinion.

05 THERAPEUTIC NEED[4,5,6,7]

The objective of treatment in type 2 diabetes is to reduce morbidity and mortality, in particular using the correct glycaemic control. The short-term objective is the improvement of symptoms (thirst, polyuria, asthenia, emaciation and blurred vision) and prevention of acute complications (infections and hyperosmolar state). The longer-term objective is the prevention of chronic microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (myocardial infarction, strokes and obliterating arteriopathy of the legs) complications and reduction of mortality.

According to the HAS guidelines (2013), the glycaemic target should be individualised depending on patient profile and can therefore evolve over time. Diabetes is progressive and treatment should be regularly re-assessed in all its components: lifestyle and dietary measures, therapeutic education and drug treatment. Data from literature do not provide the opportunity of defining a lower limit for the HbA1c target. Once the target is achieved, the treatment will be adjusted on a case-by-case basis. **For most patients with type 2 diabetes, an HbA1c target ≤ 7% is recommended.** The drug treatment should be initiated or re-assessed if the HbA1c is higher than 7%.

Special cases: for patients in whom diabetes has been newly diagnosed, with a life expectancy of more than 15 years and with no history of cardiovascular events, a target ≤ 6.5% is recommended, subject to it being achieved by the implementation or reinforcement of lifestyle and dietary measures then, in case of failure, by oral monotherapy.
In a certain number of particular cases, the glycaemic target will be less demanding: age > 75 years; history of macrovascular complication; chronic renal failure; proven serious comorbidity; limited life expectancy (< 5 years); long-lasting diabetes (> 10 years) and where the target of 7% is difficult to achieve because the increase in drugs could cause severe hypoglycaemia.

The implementation of effective lifestyle and dietary measures is an essential prerequisite for glycaemic control medication.
According to the HAS good practice guidelines (2013), the strategy generally recommended is as follows:
- metformin monotherapy,
- then, dual therapy with a combination of metformin + sulfonylurea.

If the glycaemic target is not achieved despite dual therapy with metformin + sulfonylurea,

- ✓ if the deviation from the target is < 1% for HbA1c: triple therapy with metformin + sulfonylurea + alpha-glucosidase inhibitors or DPP-4 inhibitors.
- ✓ if the deviation from the target is > 1% for HbA1c, addition of insulin in combination with metformin + sulfonylurea or a GLP-1 analogue in triple therapy, if BMI ≥ 30 kg/m^2 or if the weight gain on insulin is concerning.

In patients with elevated HbA1c levels (> 9.0%), dual therapy from the outset or insulin therapy can be offered as 1st-line treatment.

[4] NICE (National Institute for Health and Clinical Excellence). NICE and diabetes: a summary of relevant guidelines. November 2009.
[5] SIGN (Scottish Intercollegiate Guidelines Network). Management of diabetes - A national clinical guideline. Guideline 116. March 2010.
[6] ADA (American Diabetes Association) and EASD (European Association for the Study of Diabetes). Inzucchi SE, Bergenstal RM, Buse JB, *et al*. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012; 35: 1364-79.
[7] Stratégie médicamenteuse du contrôle glycémique du diabète de type 2 [Treatment strategy for glycaemic control of type 2 diabetes]. Recommandations de bonne pratique de la HAS [HAS Good practice guidelines]. January 2013.

Some patients do not achieve or maintain their glycaemic targets with insulin therapy alone. It should therefore be combined with another antidiabetic. In practice, it is metformin which is widely used in combination with insulin.[8]
In rare cases of contraindication or intolerance to metformin, sulfonylureas are offered. If, with these dual therapies, targets are not achieved, the doses of insulin can be increased but this increase in dose is often associated with an increased risk of hypoglycaemia and weight gain.

According to the HAS guidelines, when starting insulin therapy, DDP-4 inhibitors should be discontinued.
If targets are not achieved with a dual therapy, the doses of insulin can be increased, but this increase in dose is often associated with an increased risk of hypoglycaemia and weight gain.
The gliptin + insulin + metformin triple therapy was not addressed in the good practice guidelines updated by HAS in January 2013 on controlling blood glucose in type 2 diabetes. **However, linagliptin[9] or sitagliptin[10] is a treatment option that can be added to the combination of insulin + metformin in patients who do not achieve or maintain glycaemic targets with a combination of insulin + metformin.** Given its low efficiency and doubts about its safety profile, the role of saxagliptin in triple therapy had not been specified by the Committee.[11]

[8] Nathan DM, Buse JB, Davidson MB, *et al.* Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2009; 52: 17-30.
[9] Transparency Committee Opinion on TRAJENTA 5 mg. 20 March 2013.
[10] Transparency Committee Opinion on JANUVIA 100 mg. 18 July 2012.
[11] Transparency Committee Opinion on ONGLYZA 5 mg. 15 May 2013.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

NAME (INN) *Company*	Same TC* Yes/No	Indication in combination with insulin	Date of opinion	Actual Benefit	Improvement in Actual Benefit (Wording)	Reimbursement Yes/No
Fixed-dose combination of DPP-4 inhibitor + metformin						
KOMBOGLYZE 2.5 mg/1000 mg Film-coated tablet saxagliptin/metformin AstraZeneca	Yes	In combination with insulin (i.e., triple therapy) as an adjunct to diet and exercise, to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus when insulin and metformin alone do not provide adequate glycaemic control	15/05/2013	**Low**	V	Yes
JANUMET/VELMETIA 50 mg/1000 mg Film-coated tablet sitagliptin/metformin MSD	Yes	As add-on to insulin (i.e., triple combination therapy […]) when stable dose of insulin and metformin alone do not provide adequate glycaemic control.	19/07/2012	**Substantial**	V in treatment	Yes
DPP-4 inhibitor						
TRAJENTA 5 mg Film-coated tablet Linagliptin Boehringer Ingelheim	No	In combination with insulin with or without metformin, when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.	20/03/2013	**Insufficient** in dual therapy with insulin **Substantial** in triple therapy (+ insulin + metformin)	V in treatment	No
ONGLYZA 5 mg Film-coated tablet Saxagliptin Astra Zeneca	No	As combination therapy with insulin (with or without metformin), when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.	15/05/2013	**Insufficient** in dual therapy with insulin **Low** in triple therapy (+ insulin + metformin)	V in treatment	Yes

NAME (INN) *Company*	Same TC* Yes/No	Indication in combination with insulin	Date of opinion	Actual Benefit	Improvement in Actual Benefit (Wording)	Reimbursement Yes/No
JANUVIA/XELEVIA 25 mg, 50 mg Film-coated tablet Sitagliptin MSD	No	As add-on to insulin (with or without metformin) when diet and exercise plus stable dose of insulin do not provide adequate glycaemic control.	19/09/2012	**Moderate** in dual therapy with insulin **Insufficient** in combination with metformin	V in treatment	50 mg: Yes 25 mg: no
JANUVIA/XELEVIA 100 mg Film-coated tablet Sitagliptin MSD	No	As add-on to insulin (with or without metformin) when diet and exercise plus stable dose of insulin do not provide adequate glycaemic control.	18/07/2012	**Insufficient** in dual therapy with insulin **Substantial** in triple therapy (+ insulin + metformin)	- V in treatment	Yes
GALVUS 50 mg Tablet Vildagliptin Novartis	No	In combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control.	Still being assessed by the Transparency Committee			

*therapeutic category

06.1 Other health technologies

Not applicable

Conclusion

The comparators listed are all clinically relevant.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

The extension of indication was approved only in Europe.

Country	REIMBURSEMENT	
	YES/NO	Population(s) That of the Marketing Authorisation or restricted
Germany	Yes (100%)	Marketing Authorisation
United Kingdom	Yes (100%)	Marketing Authorisation
Italy	In progress	-
Spain	-	-
Portugal	In progress	-

08 SUMMARY OF PREVIOUS ASSESSMENTS

✓ **EUCREAS**

Date of opinion (reason for the request)	April 29th 2009 (Inclusion)
Indication	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.
Actual Benefit	EUCREAS 50 mg/850 mg: insufficient EUCREAS 50 mg/1000 mg: substantial
Improvement in Actual Benefit	EUCREAS 50 mg/850 mg, film-coated tablet Not applicable EUCREAS 50 mg/1000 mg, film-coated tablet EUCREAS 50 mg/1000 mg, combination of fixed doses of 50 mg of vildagliptin and 1000 mg of metformin, provides no improvement in actual benefit (level V) in comparison with the concurrent use of their separate components.
Studies requested	

✓ **ICANDRA**

Date of opinion (reason for the request)	September 7th 2011 (Inclusion)
Indication	ICANDRA 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.
Actual Benefit	Substantial
IAB	ICANDRA 50 mg/1000 mg, combination of fixed doses of 50 mg of vildagliptin and 1000 mg of metformin, provides no improvement in actual benefit (level V) in comparison with the concurrent use of their separate components.
Studies requested	

09 ANALYSIS OF AVAILABLE DATA

As a reminder, the bioequivalence between the fixed-dose combination and the separate administration of each of the active ingredients of the fixed-dose combination was established.

The dossier of the company includes the results of a[12] randomised, double-blind, placebo-controlled, parallel-group study, whose primary objective was to assess the efficacy and safety over 24 weeks of vildagliptin (50 mg 2 twice per day) in combination with insulin in 449 patients with type 2 diabetes (DM2) not adequately controlled despite a stable dose of insulin (basal or pre-mixed insulin) with or without metformin.

[12] Kothny W, Foley J, Kozloversuski P, et al. Improved glycaemic control with vildagliptin added to insulin, with or without metformin, in patients with type 2 diabetes mellitus. Diabetes Obes Metab 15: 252-257, 2013.

09.1 Efficacy

Study of the efficacy and safety over 24 weeks of vildagliptin + insulin, ± metformin, in DM2 patients not adequately controlled despite a stable dose of insulin[12]

Primary objective of the study	To demonstrate superiority in terms of reduction of HbA1c compared with placebo in the complete analysis population. The analysis is also done in the two populations with and without metformin (key secondary objective).
Method	A 24-week multicentre, randomised, placebo-controlled, double-blind, parallel-group, placebo-controlled study.
Inclusion criteria	DM2 patients aged 18 to 80 years, treated with stable doses of insulin (≤ 1 U/kg/d of basal, intermediate or pre-mixed insulin) with or without metformin at a stable dose (≥ 1.5 g/d or maximally tolerated dose) for ≥ 12 weeks before the start of the study, with a HbA1c between 7.5 and 11%, a body mass index (BMI) of 22 to 40 kg/m^2 and a fasting blood sugar < 15 mmol/l.
Main non-inclusion criteria	Fasting blood sugar ≥ 15 mmol/l Acute metabolic complication Liver condition Recent cardiovascular history (myocardial infarction, coronary bypass, or stroke or transient ischemic attack in the last 6 months) Stage III or IV heart failure.
Study size and sites	67 centres in Europe, Asia, Australia, Central America.
Course of the study	After a 2-week screening period, the DM2 patients receiving a stable dose of basal, intermediate or pre-mixed insulin, with or without metformin, were randomised in a balanced manner (1:1) to receive either vildagliptin 50 mg twice daily or placebo. Patient inclusion was stratified depending on whether or not they took metformin to ensure an approximate ratio of 60/40 (60% of patients with metformin, 40% of patients without metformin). Inclusion was stratified according to the type of insulin. After randomisation and initiation of the study treatment, patients were monitored with a visit every 4 weeks (in weeks 4, 8, 12, 16, 20, and 24), and had to continue in the same way their current treatment with metformin (if applicable) and insulin (±10%) unchanged, except in case of adjustment necessary for safety reasons.
Primary efficacy endpoint	Adjusted change in HbA1c compared with baseline, at the end of the double-blind treatment period (week 24 or the last available post-randomisation assessment done before any "major change in insulin doses").
Secondary endpoints included:	Change in fasting blood sugar compared with baseline Responder rate
Calculation of the number of subjects required	The calculation of the number of subjects necessary was based on a change in HbA1c compared with baseline of 1.1% in week 24, highlighting a significant difference of 0.5% with a power of 99% and a unilateral alpha risk of 0.025 in patients treated with insulin with or without metformin. A sample of 386 patients was required (193 per group), i.e., 428 patients in order to take into account patients lost to view (about 10%). Based on a 60/40 ratio, a sample of 428 patients highlighted a significant difference of 0.5% with a power of 93% (subgroup with metformin) or 80% (subgroup without metformin) and a unilateral alpha risk of 0.025.
Statistical analysis	The primary efficacy endpoint was analysed using an analysis of covariance (ANCOVA) model with the treatment, region, use of metformin and type of insulin as factors, and the baseline HbA1c value as a covariable.

Results:

A total of 449 patients were randomised: 228 in the vildagliptin group and 221 in the placebo group.

Table 1: Analysis population – n(%)

	Vildagliptin	Placebo
Randomised	228 (100)	221 (100)
ITT population	224 (98.2)	216 (97.7)
Safety population	227 (99.6)	221 (100)
Per protocol population	206 (90.4)	196 (88.7)

A proportion of 91.2% (n=208) of patients in the vildagliptin group completed the study versus 86.4% (n=191) in the placebo group. More patients in the placebo group were lost to view (3.2% versus 0%) or discontinued the study earlier due to withdrawal of consent (5.4% versus 3.5%).
Early discontinuations due to adverse events (AEs) were 3.9% on vildagliptin and 1.8% on placebo. A single death occurred in the placebo group.

At inclusion, the demographic characteristics of the patients were comparable in both treatment groups, with a mean age of 59.2 years (30% ≥ 65 years), a proportion of obese patients of 38.3% (mean BMI 28.9 kg/m^2), a mean time of disease of 13 years and a mean baseline HbA1c of 8.8%. Fasting blood sugar was slightly higher in the vildagliptin group (9.6 versus 9.1 mmol/l).
At inclusion, treatment with insulin was comparable in the two groups: with ~60% patients on pre-mixed insulin, ~23% on basal insulin, ~17% on intermediate insulin. The mean number of injections per day (1.8 in each group), the time of treatment with insulin (4.4 years in each group), and the mean daily dose of insulin (39.9 and 41.9 units/day in the vildagliptin and placebo groups, respectively) were balanced. A total of 276 patients (61.5%) received concomitant treatment with metformin (at a daily dose of around 2 g/d) and 173 (38.5%) were treated with insulin alone.
Nearly 70% of patients in the study were on antihypertensive therapy and half were on lipid-lowering therapy (predominantly statins). Twenty-two percent of the patients included also had cardiac history.

Primary efficacy endpoint
In the study population, at week 24, treatment with vildagliptin as an add-on to a stable dose of insulin (with or without metformin) was superior to placebo on the reduction of HbA1c (reduction of -0.77% in the vildagliptin group with a difference versus placebo of -0.72±0.1% (p<0.001).

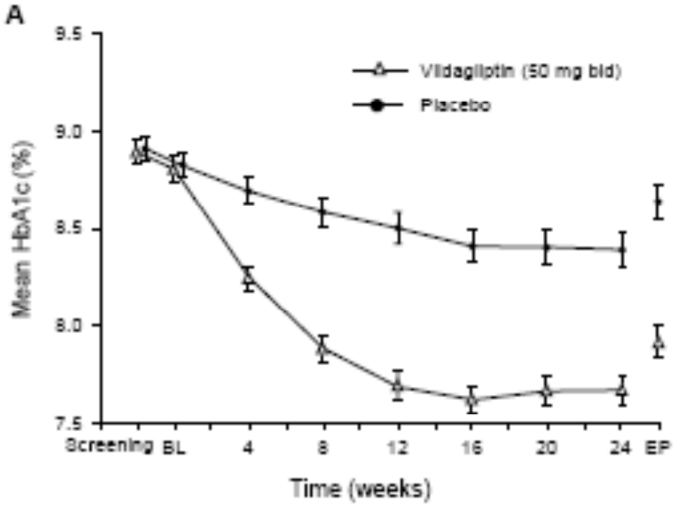

Figure 1: Mean (± SE) HbA1c during the 24 weeks of treatment in patients treated with insulin in the vildagliptin group (∆) or placebo group (●).

- Analysis in subgroups with or without concomitant metformin

The mean reduction in HbA1c versus placebo was -0.63±0.1% (p<0.001) in the subgroup of 267 patients treated in triple therapy (vildagliptin+insulin+metformin) and -0.84±0.2% (p<0.001) in the one of 169 patients on dual therapy (vildagliptin+insulin).

Table 2: ANCOVA results of the adjusted change in HbA1c compared with baseline and the end of the treatment period (total population)

				Difference in adjusted means		
Treatment	N	Mean baseline HbA1c (SE)	Adjusted mean reduction (SE)	Mean (SE)	95% CI	P
Total analysis						
Vildagliptin 50 mg 2/d	221	8.80 (0.07)	-0.77 (0.08)	-0.72 (0.10)	(-0.92, -0.52)	<0.001
Placebo	215	8.84 (0.07)	-0.05 (0.08)			
Total analysis (insulin+met)						
Vildagliptin 50 mg 2/d	133	8.78 (0.08)	-0.98 (0.09)	-0.63 (0.12)	(-0.86, -0.39)	<0.001
Placebo	134	8.80 (0.08)	-0.35 (0.09)			
Total analysis (insulin)						
Vildagliptin 50 mg 2/d	88	8.84 (0.12)	-0.60 (0.19)	-0.84 (0.19)	(-1.21, -0.47)	<0.001
Placebo	81	8.90 (0.11)	0.24 (0.20)			

Secondary endpoints

At inclusion, the mean fasting blood sugar was similar in the two groups with 9.84 mmol/l in the vildagliptin group versus 9.50 mmol/l in the placebo group. Fasting blood sugar decreased by -0.77 mmol/l in the vildagliptin group and -0.18 mmol/l in the placebo group, with a difference versus placebo of -0.59 mmol/l (p=0.05).

In the study population, the proportion of patients who achieved an HbA1c<7% was greater on vildagliptin than on placebo: 22.2% (n=49/221) versus 5.1% (n=11/214), p<0.001.

09.2 Safety/Adverse effects

9.2.1 Clinical study data

- **Study of the efficacy and safety over 24 weeks of vildagliptin + insulin, ± metformin, in DM2 patients not adequately controlled despite a stable dose of insulin[12]**

Exposure to treatment was 23.1 weeks in the vildagliptin group versus 22.8 weeks in the placebo group.

Adverse events (AEs) were reported by 57.7% of patients in the vildagliptin group and by 47.5% of patients in the placebo group (Table 3).

Table 3: Number (%) of patients reporting the most common AEs (> 4% in one of the 2 groups) (Safety Population)

	Vildagliptin 50 mgx2/day + Insulin N=227 n (%)	Placebo + Insulin N=221 n (%)
All AEs	**131 (57.7)**	**105 (47.5)**
Hyperhidrosis	26 (11.5)	28 (12.7)
Hypoglycaemia	19 (8.4)	16 (7.2)
Dizziness	18 (7.9)	19 (8.6)
Tremor	16 (7.0)	11 (5.0)
Upper respiratory tract infections	16 (7.0)	7 (3.2)
Diarrhoea	10 (4.4)	4 (1.8)
Asthenia	8 (3.5)	10 (4.5)
Fatigue	4 (1.8)	9 (4.1)

The percentage of patients who had an AE that led to discontinuation of the study was 4.0% in the vildagliptin group and 2.3% in the placebo group. SAEs were rare and similar in number between the two groups: 4.0% versus 4.1% in the vildagliptin and placebo groups, respectively. Most of the SAEs were isolated events in a single patient.
Cardio- and cerebrovascular events were confirmed by an independent adjudication committee[13] for a total of five patients: one patient (0.48%) patients in the vildagliptin group and four patients (1.8%) in the placebo group.
A single patient died during the study: a patient from the placebo group, following a ketoacidosis.
The incidence of hypoglycaemia was 8.4% on vildagliptin and 7.2% on placebo. The total number of hypoglycaemic episodes reported in the vildagliptin group (51) was higher than in the placebo group (36), the difference being primarily due to some patients having presented repeated episodes (> 2 episodes): four patients from the vildagliptin group reported a total of 35 hypoglycaemic episodes and five patients from the placebo group had 24 episodes. Most of the hypoglycaemic episodes were classified as mild (90.2% and 94.4% of hypoglycaemic episodes on vildagliptin and placebo, respectively). Severe hypoglycaemic episodes requiring the assistance of a third party were rare (two cases (0.9%) in each group).

9.2.2 Data from the last PSUR (period from 01/12/2010 to 30/11/2011)

Through the last PSUR (PSUR 6 EUCREAS), the worldwide exposure since the marketing launch can be estimated at about 1.62 million patients/year from November 2007 to November 2011 for EUCREAS (vildagliptin, metformin).

Elevated transaminases:
Cumulative data since the launch identify 200 potential cases, including 9 deaths not due to liver failure. Cases with increased transaminases greater than 10 times normal and those with characteristics consistent with drug-induced liver disease corresponded to 24 cases without distinctive individual demographic signs or medical history, or concurrent treatment. They proved reversible upon discontinuation of treatment and other possible aetiologies for reported jaundice or hepatitis were mentioned. The other 176 cases indicate an isolated elevation of transaminases without other identified factors, or cases with an obvious cause, such as pancreatic cancer, underlying liver disease, or insufficient data. Cumulative data from this PSUR highlight a small

[13] An independent adjudication committee (comprised of five cardiologists and a neurologist) prospectively evaluated, without unblinding the treatment, any potential cardio- and cerebrovascular (CCV) event that occurred in the phase III clinical trials of the development plan.

number of severe hepatic events in the marketing conditions, and these have not been associated with severe liver impairment, transplantation, or death. The evolution, when reported, is reversible.

Angioedema:
Cumulatively, analysis of the PSUR identified 540 potential cases. Only 32 cases of angioedema were identified following medical review, including three with anaphylactic reaction. Analysis of the angioedema cases is made difficult by the lack of information about treatment with ACE inhibitors or other inhibitors of the renin-angiotensin system. The 508 remaining cases were selected due to isolated urticaria or other associated events such as cardiac events. A significant number of cases of angioedema mention concomitant treatment with an ACE inhibitor or other inhibitor of the rennin-angiotensin system.

Acute pancreatitis:
Cumulatively, 145 potential cases were identified. Of the 61 cases reporting acute pancreatitis or pancreatitis, 58 were post-marketing notifications (i.e., a reporting rate of 0.036 per 1000 patients-year). The majority of cases had risk factors such as chronic pancreatitis, cholelithiasis, hypertriglyceridaemia, obesity, and alcohol use. The other cases (not labelled pancreatitis) involved elevated lipase and/or amylase (n=37) or cases of elevated transaminases.
The reporting rate of pancreatitis does not seem to show an increase in the different PSURs in a population otherwise predisposed to the onset of pancreatitis, due to diabetes-related comorbidities (hypertriglyceridaemia, cholelithiasis, and obesity).

Skin lesions:
Five hundred one potential cases were identified, including 476 spontaneous reports. Two cases of Stevens-Johnson syndrome were reported with concomitant use of allopurinol. Six cases of vasculitis, 8 skin rashes, 6 skin infections, 6 cases of exfoliative lesions, and 4 cases of skin ulcer and 3 mouth ulcers were reported. Additionally, 10 cases of bullous pemphigoid and 18 bullous lesions were reported. It should be noted that skin lesions encountered in diabetes, regardless of any treatment, are numerous. The number of cases reported by selecting their clinical relevance given that expected for diabetes seems low, considering the exposure.

Serious infections:
The cumulative analysis of cases identified 218 potential cases, including 105 serious cases (45 medically confirmed). Of the 20 deaths recorded, almost half were due to pneumonia. None of the deaths was considered to be treatment-related, or there was not enough information to assess the causality. The reporting rate for serious infections in PSUR 6 EUCREAS/ICANDRA was 0.12 per 1000 patients-year. The infections encountered were the usual infections in the general population or diabetic population, and were not rare or opportunistic infections.

Impaired cardiac function:
Since the marketing launch, 112 potential cases were identified, including 48 involving only peripheral oedema without any other associated cardiac symptom. Of the rest, 28 were reported as part of a disease other than cardiac disease, 19 were angioedema, and finally the last group of 17 cases was distributed into undocumented events, or events with a confusion factor such as significant comorbidities (heart failure or coronary heart disease, hypertension).

Muscular events with or without use of statin:
Cumulatively, 49 potential cases were identified. Of the 7 cases selected as having a particular interest in terms of signal either because of increased CPK or a diagnosis of rhabdomyolysis, only one case had statin treatment and reported a myocardial infarction. Of the 6 other cases, 2 had a treatment known to potentially lead to rhabdomyolysis.

Hypoglycaemia:
Since the marketing launch, 189 cases of hypoglycaemia have been identified, including 48 serious cases with 25 meeting the RMP definition of severity. The majority of these latter cases mentioned the use of insulin, sulfonylureas, alcohol, or indicated a fast, exercise, or an incorrect dose of the treatment. Most of the evolutions reported healing, some with discontinuation of

EUCREAS/ICANDRA or other diabetes treatments. Only a few cases required oral or intravenous sucrose.

Neuropsychiatric events (depression):
Cumulative research identified 63 potential cases. Primarily, these were depressive events, anxiety, nervousness, or memory problems. The analysis of cases retained in particular 3 cases of depression/suicidal ideation, including 2 with positive re-challenge, for which a causal relationship could not be excluded. As for the other cases, many confounding factors were associated with the events that did not seem to have a causal relationship with EUCREAS/ICANDRA.

9.2.3 SPC data

- **Adverse effects reported in patients who received 100 mg of vildagliptin daily in combination with insulin (with or without metformin) in the double-blind studies (N=371):**

Metabolism and nutrition disorders
Common Decreased blood glucose
Nervous system disorders
Common Headache, chills
Gastrointestinal disorders
Common Nausea, gastro-oesophageal reflux
Uncommon Diarrhoea, flatulence

- **Post-marketing adverse effects**

Gastrointestinal disorders
Undetermined Pancreatitis
Hepatobiliary disorders
Undetermined Hepatitis (reversible after discontinuation of the medicine)
Liver function test abnormalities (reversible after discontinuation of the medicine)
Skin and subcutaneous tissue disorders
Undetermined Urticaria
Bullous or squamous skin lesions.

9.2.4 RMP data[14]

The identified risks are: elevated transaminases and drug-induced liver injury, angioedema, acute pancreatitis, skin lesions, hypoglycaemia, lactic acidosis.
The potential risks are: serious infections, cardiac events in patients with heart failure (NYHA III), muscular events with or without the use of statin, neuropsychiatric events, and breast cancer.

9.2.5 National monitoring

In France, in the extension of the European RMP, the ANSM has implemented national monitoring of incretin mimetics. In this context, the pharmacovigilance technical committee[15] (TC) reiterates that "Diabetes is a disease at excess risk of pancreatitis or pancreatic cancer. Following the publication of Butler *et al*[16] in March 2013, highlighting in a very limited series of autopsies, a pancreatic alpha- and beta-cell hyperplasia with cell proliferation of the pancreas of diabetic patients treated with incretins compared with non-diabetic subjects or those treated with other substances, an arbitration procedure according Article 5.3 was launched in Europe to assess all

[14] Version 10.1 (8 August 2012)
[15] ANSM. Réunion du Comité technique de pharmacovigilance-CT012013043. 18 June 2013.
[16] Marked Expansion of Exocrine Pancreas with Incretin Therapy in Humans with Increased Exorcine Pancreas Dysplasia and the Potential for Glucagon-Producing Neuroendocrine Tumors. Diabetes. March 2013.

preclinical elements, clinical trials and pharmacovigilance reports on the risk of pancreatitis and pancreatic cancer. Concerning the risk of pancreatic cancer, and in the absence of sufficiently robust scientific evidence, addition of the mention of "cancer" in the SPC was not retained by the members of the TC. The results of long-term studies of morbidity and mortality and cardiovascular safety are still pending, under which the complete pancreatic safety elements should be added".

09.3 Usage/prescription data

According to the data from the IMS Winter 2013 panel as a manual moving annual total, EUCREAS was the subject of 605,575 prescriptions. The proprietary medicinal product ICANDRA does not appear in the panel.

09.4 Summary & discussion

In the extension of the indication of EUCREAS/ICANDRA in triple therapy in combination with insulin in type 2 diabetes, data is available on the free vildagliptin-metformin combination in a study of vildagliptin in combination with insulin therapy, with or without metformin. This is a randomised, double-blind, placebo-controlled study in 449 patients with type 2 diabetes inadequately controlled on insulin, with or without metformin.
The patients included had a mean age of 59.2 years (30%≥65 years) and 38.3% were obese.
The average HbA1c level on inclusion was 8.8%.
All patients were being treated with insulin. The time of treatment with insulin was 4.4 years in each group. Only 61.5% of the patients (n=276) included were on a dual therapy with insulin + metformin (about 2 g/d). The proportion of patients included falling under the fixed-dose combination, i.e., patients treated with 2 g per day of metformin, is not known. A comparison group with an optimised insulin therapy regimen would have been useful in determining the addition of vildagliptin in combination with insulin and metformin.

After 24 weeks of treatment, the reduction in HbA1c level was greater in patients on vildagliptin + insulin ± metformin than in those on placebo + insulin ± metformin (difference between vildagliptin and placebo: -0.72%, 95%CI [-0.92; -0.52]; p<0.001).
According to a subgroup analysis, the mean reduction in HbA1c versus placebo was:
- -0.63±0.1% (p<0.001) in the subgroup of 267 patients on vildagliptin in triple therapy (+insulin+metformin),
- -0.84±0.2% (p<0.001) in the subgroup of 169 patients on vildagliptin in dual therapy (+insulin).

Regarding secondary endpoints, in the overall study population, fasting blood sugar decreased in the vildagliptin group compared with the placebo group (difference versus placebo: -0.59 mmol/l (p=0.05)). The rate of responder patients (rate of HbA1c < 7%) was greater on vildagliptin than on placebo with 22.2% versus 5.1% (p<0.001).

Adverse events (AEs) were reported by 57.7% of patients in the vildagliptin group and by 47.5% of patients in the placebo group. The most common adverse events (> 5% of patients) observed in the vildagliptin group were hyperhidrosis, hypoglycaemia, dizziness, tremors, and upper respiratory infection.
The incidence of hypoglycaemia was 8.4% on vildagliptin and 7.2% on placebo. Episodes of severe hypoglecaemia were rare (two cases (0.9%) in each group).

In triple therapy in combination with insulin and metformin, it is impossible to assess patients with severe renal impairment, since metformin is contraindicated in these patients.
There is no comparative clinical study versus triple therapies that allows the comparative efficacy and safety of this fixed-dose combination to be assessed.
It is not possible, based on the available data, to assess the benefit of this fixed-dose combination compared with separate administration of the two active ingredients.

09.5 Planned studies

In its opinion of 10 December 2008, the Transparency Committee asked a study to be carried out in a representative sample of French type 2 diabetes patients, treated with GALVUS. The objectives of the VILDA observational study are to describe in real treatment situation over 2 years:
- the characteristics of the patients treated with GALVUS or EUCREAS (including age, the HbA1c value at the start of treatment, and renal, hepatic and cardiac function);
- the conditions of use of GALVUS or EUCREAS (indication, dosage, concomitant treatments, etc.);
- the level of maintenance of treatment;
- the frequency of treatment discontinuations and the reasons for them;

- the change in the HbA1c value and weight, and the occurrence of hypoglycaemia, in the long term (2 years).

The final report from this study was submitted and will be examined by the Transparency Committee as part of the renewal of inclusion of GALVUS/JALRA.

010 THERAPEUTIC USE

Vildagliptin is a treatment option in triple therapy that can be added to the combination of insulin + metformin in patients who do not achieve or maintain glycaemic targets with a combination of insulin/metformin.
The fixed-dose combination is reserved only for patients treated with a maximum dosage of 1000 mg of metformin administered twice per day. The dose of metformin in the fixed-dose combination limits therapeutic adjustments.

This therapeutic situation (triple therapy with gliptin in combination with insulin and metformin) is for patients who cannot be treated with a sulfonylurea.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual benefit

◗ Type 2 diabetes is a chronic disease with potentially serious complications, particularly cardiovascular complications.
◗ EUCREAS/ICANDRA is used in the context of treatment for hyperglycaemia.
◗ As no study has been done with the fixed-dose vildagliptin/metformin combination, the efficacy/adverse effects ratio cannot be qualified.
◗ **Therapeutic alternatives do exist**.

Public health benefit:
The public health burden of type 2 diabetes is substantial because of its high prevalence, which is constantly increasing, and the associated microvascular and macrovascular complications. The public health burden in the subpopulation of patients with an indication for EUCREAS/ICANDRA in triple therapy with insulin is considered to be moderate.
The improvement of the therapeutic management of type 2 diabetics is a public health need which is an established priority.[17] Access to effective treatments which are well tolerated in type 2 diabetes patients is a public health need.
The proprietary medicinal product EUCREAS/ICANDRA is not likely to present a public health benefit for this extension of indication in oral triple therapy with insulin, considering the lack of additional impact on public health criteria (morbidity and mortality data, improvement of quality of life) compared with the current treatment for type 2 diabetes.

Consequently, the Committee considers that the actual benefit of EUCREAS/ICANDRA is moderate in triple therapy with insulin as an adjunct to diet and exercise to improve glycaemic control in patients when a stable dose of insulin and metformin alone do not provide adequate glycaemic control.

The Committee recommends inclusion of EUCREAS/ICANDRA on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in this extension of the indication and at the dosages in the Marketing Authorisation.

◗ **Proposed reimbursement rate: 30%**

[17] Objective 55 of the Law of 9 August 2004 relating to public health policy: Reducing the frequency and severity of the complications of diabetes and particularly cardiovascular complications, a national improvement plan for the quality of life of persons with from chronic diseases 2007-2011.

011.2 Improvement in actual benefit (IAB)

As there are no direct comparisons with validated and available triple therapies, and as there is no clinical study with the fixed-dose combination, the Transparency Committee considers that EUCREAS/ICANDRA does not provide any improvement in actual benefit (level V, non-existent) in the treatment of patients with type 2 diabetes in triple therapy in combination with insulin.

011.3 Target population

The target population is patients with type 2 diabetes treated with vildagliptin **in triple therapy as an add-on to insulin and metformin,** in patients who do not achieve or maintain glycaemic targets on a combination of insulin + metformin and cannot be treated with sulfonylurea.

The target population of DPP-4 inhibitors in combination with insulin and metformin (**triple therapy**) would be about **113,000 patients.**[18]

The target population of EUCREAS/ICANDRA in combination with insulin, lies within this population.

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

Appropriate for the prescribing conditions as regards the indication, dosage and treatment duration.

[18] Transparency Committee Opinion of 20 March 2013 – TRAJENTA.