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)
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)
Indication concerned	"**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**."

Actual Benefit	**Substantial**
IAB	**As there are no direct comparisons with validated and available triple therapies, and as no clinical study has been done 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 oral triple therapy, in combination with a sulfonylurea.**
Therapeutic use	**EUCREAS/ICANDRA, fixed-dose vildagliptin/metformin combination, should be used as an adjunct to diet and exercise in combination with a sulfonylurea when dual therapy with metformin and sulfonylurea, with diet and exercise, does not provide adequate glycaemic control.** **The dose of metformin in the fixed-dose combination limits therapeutic adjustments. This fixed-dose combination is reserved only for patients treated with a maximum dosage of 1000 mg of metformin administered twice per day.**
Recommendations	**-**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (Centralised procedure)	Start date (EUCREAS): 14 November 2007 Start date (ICANDRA): 01 December 2008 Extension of indication (EUCREAS): 25 October 2012 Extension of indication (ICANDRA): 29 October 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/ICANDRA 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/ICANDRA should not be used in patients whose creatinine clearance is < 60 ml/minute.
This application concerns the use of EUCREAS/ICANDRA **in combination with a sulfonylurea (oral triple therapy),** in patients inadequately controlled with metformin and a sulfonylurea. The extension of indication in combination with insulin is the subject of a separate opinion.

By letter dated 2 July 2013, the Transparency Committee informed all distributors using incretins (gliptins and GLP-1 analogues) of their 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 12 March 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 had particularly motivated the re-assessment) 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 Feb 27; 370(9): 794-7.

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**.
- 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.[3]"

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 with metformin and a sulfonylurea:
The doses of EUCREAS/ICANDRA should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When EUCREAS/ICANDRA is used in combination with a sulfonylurea, a lower dose of the sulfonylurea may be considered to reduce the risk of hypoglycaemia.
…
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.

[3] 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 (2013) guidelines, 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 lifestyleand dietary measures then, in case of failure, by oral monotherapy.
In a certain number of special 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% proves 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.

Drug strategy:
According to the HAS (2013) good practice guidelines, 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, add 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.

[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.

Thus, good practice guidelines provide for the possibility of using a DPP-4 inhibitor in triple therapy (in combination with metformin and a sulfonylurea). Only sitagliptin is currently reimbursed in this indication.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

NAME (INN) *Company*	Same TC* Yes/No	Indication in triple therapy with sulfonylurea	Date of opinion	Actual Benefit	Improvement in Actual Benefit (Wording)	Reimbursement Yes/No
Fixed-dose combination of DPP-4 inhibitor + metformin						
JENTADUETO 2.5 mg/1000 mg Film-coated tablet Linagliptin/metformin *Boehringer Ingelheim*	Yes	In combination with a sulfonylurea (i.e., triple combination therapy), as an adjunct to diet and exercise in adult patients inadequately controlled on their maximally tolerated dose of metformin and a sulfonylurea.	05/09/2012	**Substantial**	V	No
KOMBOGLYZE 2.5 mg/1000 mg Film-coated tablet Saxagliptin/metformin *AstraZeneca*	Yes	In combination with a sulfonylurea (i.e., triple combination 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 the maximally tolerated dose of both metformin and the sulfonylurea does not provide adequate glycaemic control.	Still being assessed by the Transparency Committee	-	-	Not in triple therapy
JANUMET 50 mg/850 mg Film-coated tablet Sitagliptin/metformin *MSD*	Yes	In combination with a sulfonylurea (i.e., triple combination therapy) in patients inadequately controlled on their maximal tolerated dose of metformin and a sulfonylurea.	29/04/2009	**Insufficient**	-	No
JANUMET/VELMETIA 50 mg/1000 mg Film-coated tablet Sitagliptin/metformin *MSD*	Yes	In combination with a sulfonylurea (triple therapy) in patients inadequately controlled on their maximal tolerated dose of metformin and a sulfonylurea.	29/04/2009	**Substantial**	V	Yes

NAME (INN) *Company*	Same TC* Yes/No	Indication in triple therapy with sulfonylurea	Date of opinion	Actual Benefit	Improvement in Actual Benefit (Wording)	Reimbursement Yes/No
DPP-4 inhibitor						
TRAJENTA 5 mg Film-coated tablet Linagliptin Boehringer Ingelheim	Yes	Treatment of type 2 diabetes mellitus to improve glycaemic control in adults:[8] In combination with a sulfonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.	20/06/2012	**Substantial**	V	No
ONGLYZA 5 mg Film-coated tablet Saxagliptin Astra Zeneca	Yes	In adult patients aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control:[9] In triple oral therapy in combination with metformin plus a sulfonylurea when this regimen alone, with diet and exercise, does provide adequate glycaemic control.	Still being assessed by the Transparency Committee	-	-	Not in triple therapy
JANUVIA/XELEVIA 25 mg, 50 mg[10] Film-coated tablet Sitagliptin MSD	Yes	In triple oral therapy in combination with a sulfonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.	19/09/2012	**Insufficient** because metformin is contraindicated in renal impairment	-	Not in triple therapy
JANUVIA/XELEVIA 100 mg Film-coated tablet Sitagliptin MSD	Yes	In triple oral therapy in combination with a sulfonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.	24/06/2009	**Substantial**	V	Yes
GALVUS 50 mg Tablet Vildagliptin *Novartis*	Yes	In triple oral therapy, in combination with a sulfonylurea and metformin, when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.	Still being assessed by the Transparency Committee	-	-	Not in triple therapy

*Therapeutic category

[8] Linagliptin (TRAJENTA 5 mg) can be used in type 2 diabetes patients with renal impairment without dose adjustment.
[9] The dose of saxagliptin (ONGLYZA) should be reduced to 2.5 mg once per day in patients with moderate or severe renal impairment. This dosage is not available in France.
[10] Adjusted doses for patients with renal impairment. The 25 mg dosage is not marketed in France.

06.2 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)	29 April 2009 (Inclusion)
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.
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)	07 September 2011 (Inclusion)
Indications	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

09.1 Efficacy

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

The applicant dossier includes the results of a randomised, double-blind, placebo-controlled study whose objective was to demonstrate the efficacy and safety over 24 weeks of the addition of vildagliptin (50 mg x 2/day) to a treatment with sulfonylurea (glimepiride) and metformin not providing adequate glycaemic control.[11]

09.2 Efficacy

Primary objective of the study	To demonstrate the efficacy and safety of use over 24 weeks of the addition of vildagliptin (50 mg x2/d) to treatment with sulfonylurea (glimepiride) and metformin not providing adequate glycaemic control.
Method	A 24-week randomised, double-blind, parallel-group, placebo-controlled superiority study
Main inclusion criteria	Type 2 diabetes patients 18 to 80 years of age, not adequately controlled by oral blood glucose lowering drugs at stable doses for ≥ 12 weeks before the start of the study, with an HbA1c at randomisation between 7.5 and 11%, a body mass index (BMI) of 22 to 45 kg/m^2, and a fasting blood sugar < 15 mmol/l (during screening and randomisation).
Main non-inclusion criteria	History of acute metabolic complication History of liver disorder Recent cardiovascular history (infarction, bypass, or stroke in the last 6 months) Stage III or IV heart failure.
Study size and sites	40 sites in Europe (Germany, Italy, Hungary, Romania, United Kingdom), India, Asia, Australia, Central America.
Treatment groups	Eligible patients were randomised in a balanced manner to receive vildagliptin (50 mg x 2/d) or placebo, in addition to their existing treatment with metformin (≥ 1500 mg) and glimepiride (≥ 4 mg).
Course of the study	An initial 1- to 2-week screening period was followed by a titration and/or stabilisation period that could last up to 12 weeks, and finally the 24-week randomised, double-blind treatment period. Eligible patients were randomised and then monitored with four study visits (at weeks 6, 12, 18 and 24). The treatment with oral blood glucose lowering drugs received before screening could be metformin alone (≥ 1500 mg/d with HbA1c ≥ 8.5% and ≤ 11%) or metformin (≥ 1500 mg/d) in dual therapy with a sulfonylurea or a glinide or a glitazone (HbA1c ≥ 7.5% and ≤ 11%). Eligible patients then continued their treatment with metformin ≥ 1500 mg/d and the treatment with oral blood glucose lowering drugs other than glimepiride was modified for the 12-week titration and stabilisation period. Glimepiride was gradually titrated from 2 to 4 mg over 2 weeks and stable for 10 weeks prior to randomisation. Patients for whom the dose could not be titrated to 4 mg left the study. At the end of the stabilisation period, a visit was held (week -1) to re-evaluate eligibility based on the criteria of HbA1c ≥ 7.5 and ≤ 11% in particular.
Primary efficacy endpoint	At 24 weeks, adjusted change in **HbA1c**

[11] Lukashevich V et al. Efficacy and safety of vildagliptin in patients with type 2 diabetes mellitus inadequately controlled with dual combination of metformin and sulfonylurea. Diabetes Obes Metab 16:403-409, 2014.

Secondary endpoints included:	Change in fasting blood sugar compared with baseline Rate of responders reaching HbA1c glycaemic targets < 7% or ≤ 6.5%.
Calculation of the number of subjects required	A sample of 290 patients (145 per group) highlights a superiority of vildagliptin over placebo in the reduction of HbA1c at week 24 compared with baseline, with a difference versus placebo of 0.5%, an estimated 15% of patients lost to view, a power of 90%, a unilateral risk of 2.5%, and a standard deviation of 1.2%.
Statistical analysis	The primary efficacy endpoint was analysed using an analysis of covariance (ANCOVA) model with the treatment, region, and baseline HbA1c value as covariables. Secondary endpoints were analysed using the same ANCOVA model.

Results:

A total of 318 patients were randomised: 158 in the vildagliptin group and 160 in the placebo group.

Table 1: Populations analysed

	Vildagliptin	Placebo
Randomised	158 (100)	160 (100)
ITT population*	152 (96.2)	160 (100)
Safety population	157 (99.4)	160 (100)
Per protocol population	144 (91.1)	155 (96.9)

**Randomised population that received at least one dose of study treatment and for whom at least one efficacy measurement is available*

The percentage of patients in the vildagliptin group who completed the study was 91.1% (n=144) and that of the placebo group was 96.9% (n=155). More patients in the vildagliptin group discontinued the study early due to withdrawal of consent (4.4% vs 1.3%).

At baseline, the demographic characteristics of the patients in the two treatment groups were comparable. Patients had a mean age of 55 years (20% ≥ 65 years). The mean BMI was 28 kg/m^2 (proportion of obesity 27.4%). Patients had been suffering from the disease for an average of 7.3 years. The mean baseline HbA1c was 8.7% in the vildagliptin group and 8.8% in the placebo group. The fasting blood sugar was 9.3 mmol/l in the vildagliptin group and 9.5 mmol/l in the placebo group.

A majority of patients (n=122/158 in the vildagliptin group and n=132/160 in the placebo group) was treated with metformin (≥ 1500 mg/d) in dual therapy with glimepiride prior to inclusion in the study. Patients had been on treatment with metformin for a similar length of time in the two groups (43.8 months in the vildagliptin group and 41.3 months in the placebo group) at a comparable mean dose (1790 mg/d and 1769 mg/d respectively). Patients had been on treatment with glimepiride for 26.5 and 25.7 months respectively; and the daily dosage was 4.4 vs 4.5 mg/day. Four patients in each group were on metformin as monotherapy as basic treatment prior to the study; metformin was taken as dual therapy with another sulfonylurea at inclusion into the study for 32 patients from the vildagliptin group and 27 patients from the placebo group.

Primary efficacy endpoint: change in HbA1c at week 24

In the ITT population, a more substantial decrease in HbA1c was seen in the vildagliptin 50 mg x 2/d as add-on to metformin and glimepiride group, compared with the placebo group, with -1.01% versus -0.25% (Difference versus placebo of -0.76% 95% CI [-0.98; -0.53] p<0.001).

Table 2: Results for the primary efficacy endpoint

Treatment	n	mean baseline HbA1c (SE)	Adjusted mean reduction (SE)	Vildagliptin-Placebo difference in adjusted means		
				Mean (SE)	(95% CI)	p
ITT						
Vildagliptin + Met + Glim	152	8.75 (0.07)	-1.01 (0.09)	-0.76 (0.12)	(-0.98, -0.53)	<0.001
Placebo + Met + Glim	160	8.80 (0.07)	-0.25 (0.09)			

Glim: glimepiride Met: metformin

Secondary endpoints

The proportion of patients who achieved a target HbA1c < 7% was higher on vildagliptin than on placebo: 28.3% (43/152) vs 5.6% (9/160) (p<0.001). This was the same for the proportion of patients who achieved an HbA1c ≤ 6.5% with 13.2% (20/152) on vildagliptin compared with placebo 1.3% (2/160) (p<0.001).

Fasting blood sugar decreased in the group treated with vildagliptin by -1.11 mmol/l, while it barely changed in the placebo group (+0.02 mmol/l), with a difference versus placebo of -1.13 mmol/l 95% CI [-1.65; -0.60] (p<0.001).

The mean weight changed very little during the study, with an initial weight in the vildagliptin and placebo groups of 73.1 kg and 72.4 kg respectively, and end-of-study weights of 73.7 kg and 72.3 kg respectively.

09.3 Safety/Adverse effects

9.3.1 Clinical safety data versus placebo of the addition of vildagliptin to treatment with a sulfonylurea and metformin over 24 weeks

Exposure was similar in the two groups: 23.1 weeks on vildagliptin and 24.0 weeks for placebo. Adverse events (AEs) were reported by 50.3% of patients in the vildagliptin group and by 47.5% of patients in the placebo group. The majority of AEs were mild. The most frequently reported AEs in the vildagliptin group were dizziness (7.0% versus 1.9%), hyperhidrosis (6.4% versus 0.6%), and urinary tract infections (6.4% versus 8.1%).

Table 3: Most common AEs (≥ 5% in one of the two groups) (Safety Population)

	Vildagliptin 50 mgx2/day+ Metformin + Glimepiride N=157 n (%)	Placebo + Metformin + Glimepiride N=160 n (%)
- All AEs	**79 (50.3)**	**76 (47.5)**
Dizziness	11 (7.0)	3 (1.9)
Hyperhidrosis	10 (6.4)	1 (0.6)
Urinary tract infection	10 (6.4)	13 (8.1)
Headaches	8 (5.1)	6 (3.8)
Hypoglycaemia	8 (5.1)	3 (1.9)
Upper respiratory tract infections	8 (5.1)	3 (1.9)
Asthenia	7 (4.5)	3 (1.9)
Tremor	7 (4.5)	2 (1.3)

The percentage of patients with an AE leading to study discontinuation was low with 0.6% on vildagliptin (n=1) (pruritus resolved upon discontinuation of treatment) and 1.3% on placebo (n=2).

Serious adverse events (SAEs) were rare and reported by a similar percentage of patients in both groups: 1.9% (n=3) in the vildagliptin group and 1.3% (n=2) in the placebo group. All SAEs were isolated events in a single patient. An SAE of hypoglycaemia occurred in the vildagliptin group with a patient in a post-surgical period with reduced food intake, not treatment-related in the opinion of the investigator.
A single patient (in the placebo group) died during the study (suicide).
An independent adjudication committee 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. A single event (acute coronary syndrome) was confirmed by this committee in a patient from the vildagliptin group.
Other adjudication committees were then set up to review all important pre-specified hepatic events, as well as events that could potentially be an angioedema (review of skin, vascular, muscular, and oedema AEs).
All severe or clinically significant AEs are summarised in Table 4.

Table 4: Number (%) of patients reporting clinically significant AEs (Safety Population)

Category	Vilda + Met + Glim N=157 n (%)	Placebo + Met + Glim N=160 n (%)
Death	0 (0.0)	1 (0.6)
Serious adverse event	3 (1.9)	2 (1.3)
AE with study discontinuation	1 (0.6)	2 (1.3)
Cardio- and cerebrovascular AE*	1 (0.6)	0 (0.0)
Significant hepatic AE*	0 (0.0)	0 (0.0)
Skin, vascular, muscular, oedema AE*	0 (0.0)	0 (0.0)
AE of predefined risks	34 (21.7)	37 (23.1)

* Patients with event confirmed by the adjudication committee

The rate of hypoglycaemia was higher in the vildagliptin group than in the placebo group (5.1% (n=8) versus 1.9% (n=3)). A single patient (0.6%) from the vildagliptin group reported an episode of severe hypoglycaemia.

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

The company has provided data from the last international PSUR of EUCREAS/ICANDRA, covering the 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 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:
Since the marketing launch, 501 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:
Cumulatively, 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.

9.3.2 SPC data

- **Adverse effects reported in patients who received 50 mg of vildagliptin twice daily in combination with metformin and a sulfonylurea (N=157)**

Metabolism and nutrition disorders
Common Hypoglycaemia
Nervous system disorders
Common Feelings of vertigo, tremor
Skin and subcutaneous tissue disorders
Common Hyperhidrosis
General disorders and administration site conditions
Common Asthenia

- **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

9.3.3 RMP data[12]

Identified risks are: elevated transaminases and drug-induced liver disorders, 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.

9.3.4 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[13] (TC) reiterates that "Diabetes is a disease at excess risk of pancreatitis or pancreatic cancer. Following the publication of Butler *et al*[14] 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 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".

[12] Version 8.1 (08 August 2012)
[13] ANSM. Réunion du Comité technique de pharmacovigilance-CT012013043. 18 June 2013.
[14] 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.

09.4 Usage/prescription data

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

09.5 Summary & discussion

The dossier of the company is based on the same data as those provided for the extension of therapeutic indication of GALVUS (vildagliptin) in combination with metformin and a sulfonylurea, i.e. a randomised, placebo-controlled, double-blind, parallel-group study the aim of which was to demonstrate the efficacy and safety over 24 weeks of the addition of vildagliptin (50 mg twice/day) to treatment with sulfonylurea (glimepiride) and metformin not providing adequate glycaemic control.

No study has been performed with the fixed-dose combination of vildagliptin/metformin.

A total of 318 patients were randomised: 158 in the vildagliptin group and 160 in the placebo group.

Patients included had a mean age of 55 years (20% ≥ 65 years). The mean BMI was 28 kg/m2 (proprietary obesity of 27.4%). Patients had been suffering from the disease for an average of 7.3 years. The mean baseline HbA1c was 8.7% in the vildagliptin group and 8.8% in the placebo group. The fasting blood sugar was 9.3 mmol/l in the vildagliptin group and 9.5 mmol/l in the placebo group. The proportion of patients falling under the fixed-dose combination, i.e., those treated with 2 g/day of metformin, is not known.

After 24 weeks of treatment, a decrease in HbA1c favouring vildagliptin compared with placebo was observed in triple therapy in combination with a sulfonylurea and metformin; the difference between metformin/sulfonylurea/vildagliptin and metformin/sulfonylurea/placebo was **-0.76% 95% CI = [-0.98; -0.53%] p<0.001.**

In triple therapy, a HbA1c value < 7% was achieved by 28.3% of patients from the vildagliptin group (n=43/152) and 5.6% of patients from the placebo group (n=9/160) (p<0.001). Fasting blood sugar decreased in the group treated with vildagliptin by -1.11 mmol/l, while it barely changed in the placebo group (+0.02 mmol/l) (Difference versus placebo of -1.13 mmol/l (p<0.001)).

Adverse events (AEs) were reported by 50.3% of patients in the vildagliptin group and by 47.5% of patients in the placebo group. The majority of AEs were mild. No AE led to study discontinuation. The most frequently reported AEs in the vildagliptin group were dizziness, hyperhidrosis, and urinary tract infections.

The incidence of hypoglycaemias was 5.1% in the vildagliptin group versus 1.9% in the placebo group. None of the patients left the study due to hypoglycaemia. A single serious episode occurred in the vildagliptin group, not related to the treatment.

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 to separate administration of both active ingredients.

09.6 Planned studies

In its opinion of 10 December 2008, the Transparency Committee asked that 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 the actual treatment situation over 2 years:

- the characteristics of the patients treated with vildagliptin (including age, the HbA1c value at the start of treatment, and renal, hepatic and cardiac function);
- the conditions of use of vildagliptin (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 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

As there is no direct comparison with validated and available triple therapies, none can be preferentially recommended.
EUCREAS/ICANDRA, fixed-dose vildagliptin/metformin combination, should be used as an adjunct to diet and exercise in combination with a sulfonylurea when dual therapy with metformin and sulfonylurea, with diet and exercise, does not provide adequate glycaemic control.

The dose of metformin in the fixed-dose combination limits therapeutic adjustments. This fixed-dose combination is reserved only for patients treated with a maximum dosage of 1000 mg of metformin administered twice per day.

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.
◗ It is intended as curative therapy.
◗ As no study has been done with the fixed-dose vildagliptin/metformin combination, the efficacy/adverse effects ratio cannot be qualified.
◗ EUCREAS/ICANDRA is a treatment to use in oral triple therapy in combination with a sulfonylurea. Alternative medicinal products to this proprietary medicinal product exist.

◗ Public health benefit:
The public health burden of type 2 diabetes is considerable. The burden represented by the subpopulation of patients for whom EUCREAS/ICANDRA (triple therapy) is indicated is moderate.
Improving the therapeutic management of type 2 diabetics 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, 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 substantial in the extension of the Marketing Authorisation indication "in combination with a sulfonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled with metformin and a sulfonylurea".

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

◗ **Proposed reimbursement rate: 65 %**

011.2 Improvement in actual benefit (IAB)

As there are no direct comparisons with validated and available triple therapies, and as no clinical study has been done 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 oral triple therapy in combination with a sulfonylurea.

011.3 Target population

The target population is patients with type 2 diabetes treated with oral triple therapy with metformin + a sulfonylurea + a gliptin when dual therapy with metformin and a sulfonylurea with diet and exercise has not provided adequate glycaemic control.

The number of patients treated with dual therapy with metformin and a sulfonylurea is estimated to be 24.6% of patients treated with oral anti-diabetic drugs alone, i.e., 571,000 patients. The number of patients with an HbA1c > 7% is estimated to be 50%, according to ENTRED [National representative sample of people with diabetes] data.
The population of patients who fail properly conducted metformin and sulfonylurea dual therapy would amount to **285,000 people.**

The target population of EUCREAS/ICANDRA in triple therapy, in combination with a sulfonylurea, lies within this population.

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

Appropriate for the prescribing conditions according to the indication, dosage, and treatment duration.