HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

Opinion
23 July 2014

ONGLYZA 5 mg, film-coated tablets
B/30 (CIP: 34 009 397 358-8 7)
B/90 (CIP: 34 009 575 956-3 0)

Applicant: ASTRAZENECA

INN	saxagliptin
ATC Code (2013)	A10BH03 (Dipeptidyl peptidase 4 (DPP-4) inhibitors)
Reason for the request	**Extension of indication**
List(s) concerned	B/30 **National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2) B/90: **Hospital use** (French Public Health Code L.5123-2)
Indication concerned	**ONGLYZA is indicated in adult patients aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control:** **"- In combination with metformin and a sulfonylurea when this treatment alone, combined with diet and exercise, does not provide adequate glycaemic control."**

Actual Benefit	**Substantial**
Improvement in Actual Benefit	**In the absence of a direct comparison with validated and available triple therapies, the Transparency Committee considers that ONGLYZA does not provide an improvement in actual benefit (IAB V, non-existent) in the treatment of patients with type 2 diabetes mellitus as triple oral therapy, namely, in combination with metformin and sulfonylurea when diet and exercise plus dual therapy with these medicinal products does not provide adequate glycaemic control.**
Therapeutic use	**Saxagliptin (ONGLYZA) is a therapeutic option which can be used in combination with a sulfonylurea and metformin when diet and exercise plus dual therapy with these medicinal products does not provide adequate glycaemic control.**
Guidelines	**-**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation(centralised procedure)	Date initiated: 1 October 2009 Extension of indication: 18 February 2013 Risk management plan (RMP) + 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
	A10BH	Dipeptidyl peptidase 4 (DPP-4) inhibitors
	A10BH03	Saxagliptin

02 BACKGROUND

The ONGLYZA proprietary medicinal products are refunded in the treatment of type 2 diabetes mellitus as dual oral therapy[1] with metformin or a sulfonylurea (in cases where metformin is not appropriate) and as triple therapy with insulin and metformin.[2]
ONGLYZA is not refundable as dual therapy with insulin.[3] Since 26 July 2013, ONGLYZA also has an indication as monotherapy which is not refunded since it has not yet been assessed by the Transparency Committee.
Saxagliptin, the active ingredient of ONGLYZA, amplifies the incretin effect on the islets of Langerhan through potent and selective inhibition of dipeptidyl-peptidase (DPP-4).

This request concerns the use of ONGLYZA **as triple oral therapy, in combination with a sulfonylurea and metformin,** when this dual therapy, with diet and exercise, does not provide adequate glycaemic control.
It should be noted that the dose of ONGLYZA must be reduced to 2.5 mg once daily in patients with moderate or severe renal impairment (but this dosage is not available).

In a letter dated 2 July 2013, the Transparency Committee informed all the companies using incretin-based drugs (gliptins and GLP-1 analogues) of its desire to reassess the actual benefit, improvement in actual benefit and the target population of all the proprietary medicinal products concerned, due to reports of pancreatic damage potentially linked to these medicinal products. In this context, the Committee suspended the ongoing assessment of all files, including the ONGLYZA file.
The Committee board, in its meeting on 12 March 2014, decided not to reassess the incretin-based drugs. In fact, in the current state of knowledge and in the data available in the literature taken into account by the FDA, EMA and ANSM [French National Agency for Medicines and Health Products Safety], no evidence to date supports a link between incretin-based drugs and an increased risk of pancreatitis and pancreatic cancer which nevertheless remain risks to be monitored.[4] These risks will be the subject of increased pharmacovigilance monitoring, in morbidity-mortality clinical studies and in epidemiological studies to which the Committee will remain attentive.

[1] Transparency Committee Opinion of 2 December 2009: AB substantial - IAB level V.
[2] Transparency Committee Opinion of 15 May 2013: AB low - IAB level V.
[3] Transparency Committee Opinion of 15 May 2013: Insufficient Actual Benefit
[4] 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

"ONGLYZA is indicated in adult patients aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control:

As monotherapy[5]

- in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

as dual oral therapy,[6] in combination with

- metformin, when metformin alone, with diet and exercise, does not provide adequate glycaemic control.

- a sulfonylurea, when the sulfonylurea alone, with diet and exercise, does not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate.

- a thiazolidinedione,[7] when the thiazolidinedione alone with diet and exercise, does not provide adequate glycaemic control in patients for whom use of a thiazolidinedione is considered appropriate.

As triple oral therapy in combination with

- **metformin plus a sulfonylurea when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.**

As combination therapy with insulin (with or without metformin), when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.[8]"

04 DOSAGE

“The recommended dose of ONGLYZA is 5 mg once daily. ONGLYZA tablets must not be split or cut. When ONGLYZA is used in combination with insulin or a sulfonylurea, a lower dose of the insulin or sulfonylurea may be required to reduce the risk of hypoglycaemia.

Special populations

Elderly patients (≥ 65 years old)

No dose adjustment is recommended based solely on age. Experience in patients 75 years and over is extremely limited and particular attention is required when treating this population.

Renal impairment

No dose adjustment is recommended for patients with mild renal impairment.

The ONGLYZA dose should be reduced to 2.5 mg once daily in patients with moderate or severe renal impairment.

[5] Indication obtained prior to submission of the request for reimbursement as triple oral therapy, not yet assessed by the Transparency Committee.

[6] Indication assessed by the Transparency Committee on 02/12/2009 (AB substantial - IAB V)

[7] Indication obsolete because pioglitazone has not been marketed in France since 2011.

[8] Indication assessed by the Transparency Committee on 15/05/2013 (AB low- IAB V as triple therapy and AB insufficient as dual therapy)

Experience in patients with severe renal impairment is extremely limited. Consequently, saxagliptin must be used with caution in this population. ONGLYZA is not recommended for patients with end-stage renal disease (ESRD) requiring haemodialysis.

Because the dose should be limited to 2.5 mg based upon renal function, assessment of renal function is recommended prior to initiation of treatment, and, in keeping with routine care, renal assessment should be done periodically thereafter

Hepatic impairment
No dose adjustment is necessary for patients with mild or moderate hepatic impairment (see section 5.2). Saxagliptin should be used with caution in patients with moderate hepatic impairment, and is not recommended for use in patients with severe hepatic impairment.

Paediatric population
The safety and efficacy of ONGLYZA in children aged birth to < 18 years have not yet been established. No data are available. "

05 THERAPEUTIC NEED[9,10,11,12]

The objective of treatment in type 2 diabetes mellitus is to reduce morbidity and mortality, in particular through 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 hyperglycaemic coma). The longer-term objective is the prevention of chronic microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (myocardial infarction, strokes and peripheral arterial disease of the lower limbs) complications and reduction of mortality.

According to the HAS (2013) guidelines, the glycaemic target should be individualised depending on patient profile and can therefore change over time. Diabetes mellitus 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 does not enable a lower limit for the HbA1c target to be defined. Once the target is achieved, the treatment will be adjusted on a case by-case basis. **For most patients with type 2 diabetes mellitus, an HbA1c target ≤ 7% is recommended.** Drug treatment should be initiated or re-assessed if the HbA1c is higher than 7%.

Special cases: for patients in whom diabetes mellitus has been newly diagnosed, with a life expectancy of more than 15 years and with no history of cardiovascular events, a target of ≤ 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 special cases the glycaemic target is less demanding: age > 75 years; history of macrovascular complications; chronic renal failure; proven serious comorbidity; limited life expectancy (< 5 years); long-lasting diabetes mellitus (> 10 years) and whose target of 7% proves difficult to achieve because the increase in drugs risks inducing severe hypoglycaemia.

[9] NICE (National Institute for Health and Clinical Excellence). NICE and diabetes: a summary of relevant guidelines. November 2009.
[10] SIGN (Scottish Intercollegiate Guidelines Network). Management of diabetes - A national clinical guideline. Guideline 116. March 2010.
[11] 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.
[12] Stratégie médicamenteuse du contrôle glycémique du diabète de type 2 [Treatment strategy for glycaemic control of type 2 diabetes mellitus]. Recommandations de bonne pratique de la HAS [HAS Good Practice Guidelines]. January 2013.

Implementation of effective lifestyle and dietary measures is an essential prerequisite to drug treatment for glycaemic control.

Drug strategy:
According to the HAS good practice guidelines (2013), the generally recommended strategy is as follows:
- metformin monotherapy,
- then, dual therapy with the combination of metformin + sulfonylurea.

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

- ✓ if the difference from the target is < 1% HbA1c: triple therapy with metformin + sulfonylurea + alpha-glucosidase inhibitors or DPP-4 inhibitors.

- ✓ if the difference from the target is > 1% HbA1c, add insulin in combination with the metformin + sulfonylurea or a GLP-1 analogue in triple therapy, if BMI > 30 kg/m^2 or if weight gain on insulin is concerning.

Therefore, the good practice guidelines include the possibility of using a DPP-4 inhibitor as 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 as triple therapy with metformin and sulfonylurea	Date of Opinion	Actual Benefit	Improvement in Actual Benefit (Wording)	Reimbursement Yes/No
DPP-4 inhibitors						
TRAJENTA 5 mg Film-coated tablet Linagliptin** *Boehringer Ingelheim*	Yes	In combination with a sulfonylurea and metformin when diet and exercise plus dual therapy with these medicinal products does not provide adequate glycaemic control.[13]	20 June 2012	**Substantial**	V	No
JANUVIA / XELEVIA 25 mg, 50 mg[14] Film-coated tablet Sitagliptin** *MSD*	Yes	As triple oral therapy in combination with a sulfonylurea and metformin when diet and exercise plus dual therapy with these two medicinal products does not provide adequate glycaemic control.	19 September 2012	**Insufficient** because metformin is contraindicated in patients with renal impairment	-	Not as triple therapy
JANUVIA/XELEVIA 100 mg Film-coated tablet Sitagliptin** *MSD*	Yes	As triple oral therapy in combination with a sulfonylurea and metformin when diet and exercise plus dual therapy with these two medicinal products does not provide adequate glycaemic control.	24 June 2009	**Substantial**	V	Yes
GALVUS 50 mg tablet Vildagliptin** *Novartis*	Yes	As triple oral therapy in combination with a sulfonylurea and metformin when diet and exercise plus dual therapy with these two medicinal products does not provide adequate glycaemic control.	Still being assessed by the Transparency Committee	-	-	Not as triple therapy

*Therapeutic category ** Exists in a fixed combination with metformin

[13] Linagliptin (TRAJENTA) can be used in type 2 diabetic patients with renal impairment without dose adjustment.
[14] Dosages adjusted for patients with renal impairment. The 25 mg dose is not marketed in France.

06.2 Other health technologies

Not applicable.

Conclusion

The clinically relevant comparators are the DPP-4 inhibitor-based proprietary medicinal products indicated as triple therapy (in combination with metformin and a sulfonylurea). Only sitagliptin is currently reimbursed in this indication.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Extension of the indication has only been approved in Europe.

Country	REIMBURSEMENT	
	YES/NO	Population(s) That of the Marketing Authorisationor restricted
Germany	Yes (100%)	Marketing Authorisation
United Kingdom	Yes (100%)	As second-line treatment when sulfonylureas are contraindicated.
Italy	Yes	Marketing Authorisation
Spain	Yes	Marketing Authorisation
Portugal	In progress	-

08 SUMMARY OF PREVIOUS ASSESSMENTS

Date of opinion (reason for the request)	2 December 2009 (Inclusion)
Indication	ONGLYZA is indicated in adult patients aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control: • in combination with metformin, when metformin alone, with diet and exercise, does not provide adequate glycaemic control, • in combination with a sulfonylurea, when the sulfonylurea alone, with diet and exercise, does not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate, • in combination with a thiazolidinedione, when the thiazolidinedione alone, with diet and exercise, does not provide adequate glycaemic control in patients for whom use of a thiazolidinedione is considered appropriate.
Actual Benefit	Substantial
Improvement in Actual Benefit	ONGLYZA 5 mg does not provide any improvement in actual benefit (IAB V) in the management of patients with type 2 diabetes mellitus as dual therapy, in combination with metformin or a sulfonylurea or a glitazone.
Studies requested	The Transparency Committee would like a study to be carried out in a representative sample of French type 2 diabetic patients, treated with ONGLYZA. The aim of the study would be to describe the actual situation with regard to treatment: • the characteristics of the patients treated (including age, the HbA1c value at start of treatment, renal, hepatic and cardiac function); • the conditions under which this proprietary medicinal product is used (indication, dosage and dose adjustments, concomitant treatments, methods used to monitor blood glucose, etc.); • level of maintenance of treatment; • the frequency of treatment discontinuations and the reasons for them; • the change in the HbA1c value and weight, as well as occurrence of

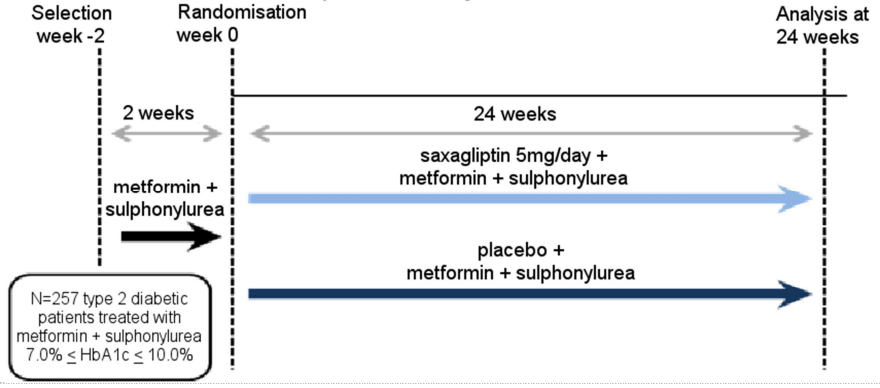
	hypoglycaemia in the long-term (2 years). Reasons should be given for choice of study duration, which should be decided on by a scientific committee, and the duration should be sufficiently long to answer the questions raised by the Transparency Committee. If planned or on-going studies, in particular within the remit of the European Risk Management Plan, do not answer all the questions raised by the Transparency Committee, a specific study must be conducted.

Date of Opinion (reason for the request)	15 May 2013 (Extension of indication)
Indication	ONGLYZA is indicated in adult patients aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as combination therapy with insulin (with or without metformin), when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.
Actual Benefit	Insufficient and provisional, pending the reassessment of gliptins as dual therapy, in combination with insulin when this regimen alone, with diet and exercise, does not provide adequate glycaemic control, for reimbursement by National Health Insurance. Low and provisional, pending reassessment of gliptins as triple therapy, in combination with insulin and metformin when this combination alone, with diet and exercise, does not provide adequate glycaemic control.
Improvement in Actual Benefit	As dual therapy in combination with insulin: not applicable As triple therapy, in combination with insulin and metformin, ONGLYZA does not provide any improvement in actual benefit (IAB V, non-existent) in the management of type 2 diabetic patients in whom this combination alone, with diet and exercise, does not provide adequate glycaemic control.
Studies requested	The Transparency Committee would like the follow-up study requested in December 2009 to be extended to the patients concerned by this extension of indication.

09 ANALYSIS OF AVAILABLE DATA

09.1 Efficacy

The company file includes results from a randomised, double-blind, placebo-controlled, phase IIIb study, in parallel groups, the objective of which was to demonstrate the efficacy and safety over 24 weeks of the addition of saxagliptin (5 mg/day) to a treatment with sulfonylurea and metformin not providing adequate glycaemic control (study D1680L00006).

Principal study objective	Compare the changes in the HbA1c level between the initiation of treatment and week 24 in patients with type 2 diabetes mellitus receiving saxagliptin 5 mg/day versus placebo, in combination with metformin and a sulfonylurea.
Method	Randomised, double-blind, placebo-controlled study with parallel groups of patients.
Study population	
Main inclusion criteria	- Patients with type 2 diabetes mellitus - Patients aged 18 to 78 years - Body mass index (BMI) ≤ 40 kg/m² - HbA1c level ≥ 7.0% and ≤ 10.0% - Stable treatment with a combination of metformin (at the maximum tolerated dose and ≥ 1,500 mg/day) and a sulfonylurea (at a maximum tolerated dose and ≥ 50% of the maximum recommended dose) for at least 8 weeks
Main non-inclusion criteria	- Symptoms linked with poor glycaemic control, including marked polyuria and polydipsia with weight loss ≥ 10% during the 3 months prior to inclusion. - History of diabetic ketoacidosis or hyperosmolar coma - Use of insulin, a DPP-4 inhibitor, GLP-1 analogue and/or another antidiabetic (other than metformin and sulfonylurea) during the 3 months prior to inclusion - Creatinine clearance estimated at < 60 ml/min - Congestive heart failure defined by an NYHA (New York Heart Association) score of class III or IV and/or a left ventricular ejection fraction of < 40%. - Active hepatic disease and/or significantly abnormal hepatic function defined as concentrations of aspartate aminotransferase and/or alanine aminotransferase > 3 times the upper limit of normal and/or serum bilirubin > 2.0 mg/dl (> 34 µmol). - Creatine kinase > 10 times the upper limit of normal
Study size and sites	35 centres in 6 countries (UK, Canada, Australia, India, Korea and Thailand).
Treatment groups	The patients were randomised (1:1) into one of the 2 groups: - saxagliptin 5 mg/day, - placebo, in combination with metformin and a sulfonylurea.
Course of the study	Patients, meeting the inclusion criteria, were previously selected and had to continue their treatment with metformin and sulfonylurea during the 2 weeks prior to randomisation. 

Primary efficacy endpoint	Change in **HbA1c level** compared with the baseline value at 24 weeks
Secondary endpoints included:	Change compared with the baseline value of: o postprandial glycaemia 2 hours after breakfast o fasting glycaemia Percentage of patients achieving the glycaemic threshold (HbA1c level < 7%) Change compared with the baseline value of the fasting concentrations of: o total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides, o insulin, C-peptide and glucagon. Change in the patients' quality of life measured with the EQ-5D questionnaire.
Calculation of the number of subjects required	To reveal an HbA1c difference of 0.40% (standard deviation 1.1%) between the 2 treatment groups on the absolute changes between the baseline value and the value at 24 weeks with a threshold of 5% and a power of 80%, 240 randomised and treated patients were required. Estimating a lost to view rate of 4%, the number of randomised patients was 250.
Statistical analysis	The main analysis of the efficacy endpoints was performed on the intention to treat population which corresponds to the patients: o randomised and having received saxagliptin or placebo at least once during the 24 weeks of the study, o and with, for at least one of the efficacy endpoints, a measurement at randomisation and at least one measurement after randomisation. The safety analysis population was made up of all the randomised patients having received saxagliptin or placebo at least once (safety analysis population). Main analysis in LOCF[15] with an ANCOVA model (adjusted according to the initial characteristics of the patients) Secondary analyses according to a hierarchical test procedure, an initial comparison should present statistically significant results ($p<0.05$) to enable the following comparison. This analysis was performed on the ITT population.

Results:

A total of 257 patients were randomised: 129 in the saxagliptin group and 128 in the placebo group.

Table 1: Analysis population - n (%)

	Saxagliptin	Placebo
Intention-to-treat (ITT) population	127 (98.4)	128 (100)
Per protocol population	108 (83.7)	112 (87.5)
Safety population	129 (100.0)	128 (100)

The percentage of patients withdrawn from the study was 12.4% (n=16) in the saxagliptin group and 11.7% (n=17) in the placebo group. The most common reason was worsening of type 2 diabetes mellitus (6.2% of patients in the saxagliptin group versus 5.5% of patients in the placebo group).

The socio-demographic and clinical characteristics of the patients at inclusion were similar between the two treatment groups, apart from the HbA1c level, the postprandial glycaemia and fasting glycaemia, which are higher in the saxagliptin group. These differences were taken into account in the statistical analysis by integrating the baseline values as covariates. The mean age of the patients was 57 years (of which 21.7% ≥ 65 years).

Table 2: Patient characteristics on inclusion

	Saxagliptin 5 mg/day (N=129)	Placebo (N=128)

[15] LOCF: Last Observation Carried Forward. These are the last available results for a given endpoint.

Age (years) mean (SD) < 65 years ≥ 65 years	 57.2 (9.55) 78.3% 21.7%	 56.8 (11.49) 74.2% 25.8%
Sex, n (%) Male Female	 80 (62.0) 49 (38.0)	 74 (57.8) 54 (42.2)
Ethnic origin, n (%) Asian Caucasian	 70 (54.3) 59 (45.7)	 71 (55.5) 57 (44.5)
Weight (kg) mean (SD)	82.4 (19.86)	80.3 (18.47)
BMI (kg/m^2) mean (SD)	29.4 (5.26)	29.1 (4.93)
HbA1c (%) mean (SD) median	 8.38 (0.856) 8.30	 8.19 (0.832) 8.10
Postprandial glycaemia (mg/dl) Missing values mean (SD) median	 7 269.18 (76.814) 265.77	 6 265.60 (69.713) 261.26
Fasting glycaemia (mg/dl) Missing values mean (SD) median	 6 162.24 (47.322) 154.95	 5 155.45 (38.370) 154.95
Dose of metformin (mg/day) mean (SD)	1,956.98 (430.92)	1,957.03 (422.02)
Dose of sulfonylurea (mg/day) **Glimepiride** number of patients n (%) mean (SD) **Gliclazide** number of patients n (%) mean (SD) **Glibenclamide** number of patients n (%) mean (SD) **Glipizide** number of patients n (%) mean (SD)	 58 (45.0) 5.21 (1.51) 57 (44.2) 157.89 (99.51) 10 (7.8) 14.50 (5.50) 5 (3.9) 20.00 (12.25)	 61 (47.7) 4.89 (1.44) 52 (40.6) 161.54 (90.02) 10 (7.8) 16.50 (5.36) 4 (3.1) 15.00 (5.77)

Primary efficacy endpoint: change in HbA1c at 24 weeks

After 24 weeks of treatment, a greater reduction in the mean adjusted HbA1c level was observed in the saxagliptin 5 mg/day group compared with the placebo group, with 0.74% versus -0.08% after adjustment for the baseline values (difference between the groups: -0.66%, 95% CI [-0.86; -0.47], p<0.0001).

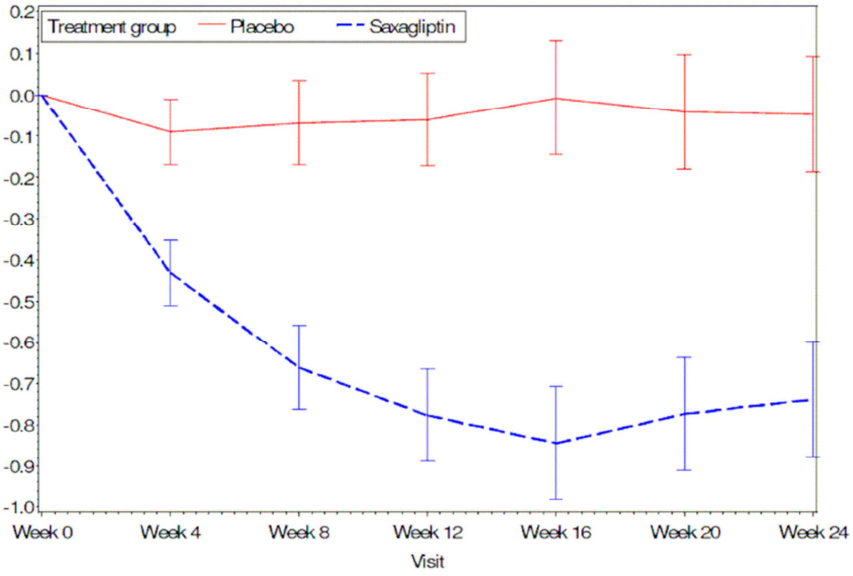
Table 3: Change in the HbA1c level (%) at 24 weeks (LOCF; ITT population)

	Saxagliptin 5 mg/day	**Placebo**
n/N analysed	127/127	127/128
Initial mean (SEM*)	8.37 (0.075)	8.17 (0.073)
Mean at week 24 (SEM*)	7.63 (0.089)	8.12 (0.098)

Change compared with baseline, Adjusted mean (SEM*) 95% CI	**-0.74 (0.075)** [-0.89; -0.60]	**-0.08 (0.074)** [-0.23; 0.07]
Difference of the adjusted mean between the treatments (SEM*) 95% CI p	**- 0.66 (0.099)** [-0.86; -0.47] <0.0001	

**Standard error of the mean*

Figure 1: Change in the adjusted mean of HbA1c (%) at 24 weeks (LOCF; ITT population)



Secondary endpoints

- *Change in postprandial glycaemia 2 hours after breakfast*

After 24 weeks of treatment, a greater reduction in postprandial glycaemia was observed in the saxagliptin group 5 mg/day than in the placebo group:
-11.66 mg/dl versus +5.08 mg/dl after adjustment for the baseline values (difference between the groups: -16.74 mg/dl, 95% CI [-31.85; -1.62], p=0.0301).

- *Change in fasting glycaemia*

After 24 weeks of treatment, there was no difference in the fasting glycaemia between the saxagliptin 5 mg/day group and the placebo group: -5.28 mg/dl versus +2.62 mg/dl after adjustment for the baseline values (difference between the treatments: -7.90 mg/dl, 95% CI [-16.96; 1.15]), NS)

- *Percentage of patients achieving the glycaemic threshold (HbA1c level < 7%)*

Insofar as no difference between the 2 groups was observed for the "change in fasting glycaemia" endpoint, the responder rate results cannot be presented.

No difference was revealed between the treatment groups for the laboratory endpoints (serum lipids, fasting serum insulin, C-peptide and glucagon) and quality of life.

09.2 Safety/Adverse effects

9.2.1 Data from the clinical study versus placebo over 24 weeks

The mean exposure to treatment during the 24 weeks of the study was comparable: 158.9 ± 31.41 days in the saxagliptin group 5 mg/day and 160.1 ± 29.73 days in the placebo group.
62.8% of patients in the saxagliptin group presented an adverse event (AE) versus 71.7% in the placebo group.
16.3% of patients in the saxagliptin group presented an AE assessed as being treatment-related by the investigator versus 10.2% in the placebo group.
The rates of AEs having resulted in study withdrawal were 0.8% in the saxagliptin group and 2.3% in the placebo group. A higher proportion of patients in the placebo group presented a serious AE (SAE) with 5.5% versus 2.3% in the saxagliptin group.

The majority of AEs were of mild to moderate intensity. No deaths were reported.

Table 4: General safety - Number of patients (%)

	Saxagliptin 5 mg/day (N=129)	**Placebo (N=128)**
Patients with at least one AE, n (%)		
Total	81 (62.8)	91 (71.7)
Treatment-related	21 (16.3)	13 (10.2)
AE-related study withdrawals, n (%)	1 (0.8)	3 (2.3)
Patients with at least one SAE, n (%)		
Total	3 (2.3)	7 (5.5)
Treatment-related	1 (0.8)	0
SAE-related study withdrawals, n (%)	0	1 (0.8)
Death	0	0

Note: hypoglycaemic episodes are included in this table

Specific safety

The results relating to certain AEs of interest are summarised in table 5.

Table 5: Specific safety - AE by target organ system; Number of patients (%)

	Saxagliptin 5 mg/day (N=129)	**Placebo (N=128)**
Hypoglycaemia, n (%)	13 (10.1)	8 (6.3)
*Confirmed hypoglycaemia**	*2 (1.6)*	*0*
Infections**, n (%)	34 (26.4)	44 (34.4)
nasopharyngitis	*8 (6.2)*	*12 (9.4)*
urinary tract infection	*4 (3.1)*	*8 (6.3)*
upper respiratory tract infection	*6 (4.7)*	*6 (4.7)*
pharyngitis	*0*	*3 (2.3)*
oral candidiasis	*0*	*3 (2.3)*
Gastrointestinal disorders, n (%)	24 (18.6)	23 (18.0)
diarrhoea	*7 (5.4)*	*5 (3.9)*
flatulence	*4 (3.1)*	*0*
gastritis	*3 (2.3)*	*3 (2.3)*
nausea	*2 (1.6)*	*4 (3.1)*
constipation	*1 (0.8)*	*3 (2.3)*
Hepatic disorders, n (%)	1 (0.8)	0
Skin and subcutaneous tissue disorders***, n (%)	0	1 (0.8)
Lymphopaenia, n	0	0
Thrombocytopenia, n	0	0

	Saxagliptin 5 mg/day (N=129)	Placebo (N=128)
Localised oedema, n (%)	0	0
Confirmed cardiovascular event, n (%)	1 (0.8)	0
Hypersensitivity reactions, n (%)	1 (0.8)	1 (0.8)
Pancreatitis, n (%)	1 (0.8)	0
Fracture, n (%)	0	1 (0.8)

* Capillary glycaemia ≤ 50 mg/dl associated with symptoms of hypoglycaemia.
** Only the infections observed in more than 5% of patients from one of the treatment groups are presented in the table.
*** Only the skin and subcutaneous tissue disorders involving at least 2 patients are presented in the table.

- Hypoglycaemia

The percentage of patients with "hypoglycaemia" (reflecting a diagnosis of hypoglycaemia) or confirmed hypoglycaemia (measured with a capillary glycaemia ≤ 50 mg/dl associated with hypoglycaemia symptoms) type AEs were slightly higher in the saxagliptin 5 mg/day group compared with the placebo group:

- 10.1% in the saxagliptin 5 mg/day group and 6.3% in the placebo group for all the "hypoglycaemia" type AEs.
- 2 patients (1.6%) in the saxagliptin 5 mg/day group and no patients in the placebo group for all the confirmed hypoglycaemic episodes.

In addition, no severe hypoglycaemia (i.e requiring medical assistance) was observed. For 1 patient in the saxagliptin 5 mg/day group and 2 patients in the placebo group, the hypoglycaemia resulted in a reduction of the sulfonylurea dose.

- Infection

The percentage of patients with an infection and invasive infection type AE was lower in the saxagliptin 5 mg/day group compared with the placebo group (26.4% versus 34.4%). The most commonly reported infections (≥ 2% of patients) were nasopharyngitis (respectively 6.2% versus 9.4%), upper respiratory tract infections (4.7% in each group), urinary tract infections (3.1% versus 6.3%), pharyngitis (0 versus 2.3%) and oral candidiasis (0 versus 2.3%).

- Gastrointestinal disorders

The percentage of patients with a gastrointestinal disorder was comparable between the 2 treatments groups (18.6% versus 18.0%). The most commonly reported disorders (≥ 2% of patients) were diarrhoea (5.4% versus 3.9%), flatulence (3.1% versus 0), gastritis (2.3% in each group), nausea (1.6% versus 3.1%) and constipation (0.8% versus 2.3%). No gastrointestinal SAE was observed and one case of abdominal distension resulted in study withdrawal in a patient from the placebo group.

- Hepatic disorder

Only one patient (0.8%) from the saxagliptin 5 mg/day group presented asymptomatic hepatitis. This was diagnosed at the last study visit and no treatment was started to manage this AE.

- Skin tolerability

One case of skin ulcer was reported in a patient from the placebo group.

- Cardiovascular adverse event

One confirmed cardiovascular AE was observed in one patient (0.8%) from the saxagliptin 5 mg/day group: one case of carotid artery occlusion, not considered to be treatment-related.

- Hypersensitivity reaction

One patient (0.8%) from each group presented a hypersensitivity reaction (urticaria). This AE was not considered to be treatment-related.

- Pancreatitis

One patient from the saxagliptin 5 mg/day group (0.8%) presented pancreatitis. During the study, this patient initially presented asymptomatic hepatitis. After the end of follow-up (day 170), asymptomatic pancreatitis of mild intensity was diagnosed due to elevated concentrations of serum lipase during a laboratory assessment. These AEs (hepatitis and pancreatitis) were both considered to be treatment-related by the investigator.

- Fracture

One patient from the placebo group (0.8%) presented a rib fracture.

- Lymphopaenia, thrombocytopaenia and localised oedema

No case was identified for these AEs during the 24 weeks of follow-up.

9.2.1 PSUR data

The company provided data from the 6 PSURs covering the period from 31 July 2009 to 30 July 2012, already assessed by the Committee as part of the extension of indication assessment in combination with insulin (see Transparency Committee opinion dated 15 May 2013).

9.2.2 SPC data

According to the SPC:
"Post-marketing experience from clinical trials and spontaneous cases

Table 2 presents additional adverse effects which were reported post-marketing. The frequencies are based on experience from clinical trials.

Table 2. Frequency of additional adverse effects by system organ class

System organ class Adverse effect	Frequency of adverse effects[1]
Gastrointestinal disorders	
Nausea	Common
Pancreatitis	Uncommon
Immune system disorders	
Hypersensitivity reactions[2] (see sections 4.3 and 4.4)	Uncommon
Anaphylactic reactions including anaphylactic shock (see sections 4.3 and 4.4)	Rare
Skin and subcutaneous tissue disorders	
Angioedema (see sections 4.3 and 4.4)	Rare
Dermatitis	Uncommon
Pruritus	Uncommon
Rash[2]	Common
Urticaria	Uncommon

[1] The estimated frequencies are based on the pooled analysis of clinical trials with saxagliptin as monotherapy, in addition to metformin and the initial combination with metformin, in addition to a sulfonylurea and in addition to thiazolidinediones.
[2] These reactions have also been identified in clinical trials before authorisation but do not correspond to the table 1 criteria.

Description of selected adverse effects

In combination with metformin and a sulfonylurea: sensation of vertigo (common), fatigue (common) and flatulence (common).

Hypoglycaemia

When used in combination with metformin and a sulfonylurea, the overall incidence of these reported cases of hypoglycaemia was 10.2% for ONGLYZA 5 mg and 6.3% for placebo."

9.2.3 Risk management plan[16]

The main identified risks are: hypersensitivity reactions, pancreatitis, infections, gastrointestinal events.
The main potential risks are: skin lesions including ulcerations, erosions and cutaneous necrosis, lymphopaenia, thrombocytopaenia, hypoglycaemia, opportunistic infections, bone fractures and severe skin reactions including Lyell's syndrome and Stevens-Johnson syndrome.

9.2.4 National monitoring

In France, in the extension of the European RMP, ANSM [French National Agency for Medicines and Health Products Safety] implemented incretin mimetic national monitoring. In this context, the pharmacovigilance risk assessment committee[17] (PRAC) [French: comité technique de pharmacovigilance] recalled that "Diabetes mellitus is a disease with increased risk of pancreatitis or pancreatic cancer. Following the publication by Butler et al.[18] in March 2013 revealing, on a very limited series of autopsies, alpha and beta pancreatic hyperplasia with cellular proliferation of the

[16] Version 2 (28 June 2012).
[17] ANSM. Meeting of the Comité technique de pharmacovigilance-CT012013043. 18 June 2013.
[18] Marked Expansion of Exocrine Pancreas with Incretin Therapy in Humans with Increased Exocrine Pancreas Dysplasia and the Potential for Glucagon-Producing Neuroendocrine Tumors.Diabetes. March 2013

pancreas in diabetic subjects treated with incretin-based drugs compared with non-diabetic patients or patients treated with other substances, an arbitration procedure according to article 5.3 has been initiated on a European level to evaluate all the preclinical elements, clinical trials and pharmacovigilance data on the risk of pancreatitis and pancreatic cancer. Concerning the risk of pancreatic cancer, and due to the absence of sufficiently robust scientific evidence, the addition of the word "cancer" in the SPC has not been supported by the C members. The results of long-term studies on morbidity and mortality and cardiovascular safety are still pending, in which all the elements of pancreatic safety must be added".

09.3 Usage/prescription data

According to IMS data (moving annual total, spring 2014), 342,071 prescriptions were written for ONGLYZA.

09.4 Summary and discussion

The company file includes results from a randomised, double-blind, placebo-controlled study, in parallel groups, the objective of which was to demonstrate the efficacy and safety over 24 weeks of the addition of saxagliptin (5 mg/day) to a treatment with sulfonylurea and metformin not providing adequate glycaemic control.

A total of 257 patients were randomised: 129 in the saxagliptin group and 128 in the placebo group.
The mean age of the patients was 57 years (23.7% ≥ 65 years). The percentage of patients withdrawn from the study in the saxagliptin group was 12.4% (n=16) and 11.7% (n=17) in the placebo group. The most common reason was worsening of type 2 diabetes mellitus (6.2% of patients in the saxagliptin group versus 5.5% of patients in the placebo group).

After 24 weeks of treatment, reduction in the HbA1c level in favour of saxagliptin compared with placebo was observed as triple therapy in combination with a sulfonylurea and metformin; the difference between metformin/sulfonylurea/saxagliptin and metformin/sulfonylurea/placebo was **-0.66% 95% CI = [-0.86; -0.47%] p<0.0001.**

As triple therapy, the change in the postprandial glycaemia measured 2 hours after breakfast was greater in the saxagliptin group than in the placebo group: -11.66 mg/dl versus +5.08 mg/dl (difference -16.74 mg/dl, p=0.0301)). No difference in the change in fasting glycaemia was revealed between the 2 groups. Usable results are not available for the responder rate (HbA1c level < 7%).

62.8% of patients in the saxagliptin group presented an adverse event (AE) versus 71.7% in the placebo group. The most commonly reported AEs in the saxagliptin group were infections (mainly nasopharyngitis, upper respiratory tract infections, urinary tract infections), gastrointestinal disorders and hypoglycaemia.

09.5 Planned studies

The results of the phase IV, randomised, double-blind, placebo-controlled clinical study (SAVOR) on the effect of saxagliptin on the incidence of cardiovascular events in 16,500 patients with type 2 diabetes mellitus with a 5 year follow-up are being assessed by the EMA.

The results of the phase IIIb/IV, randomised, double-blind, glimepiride-controlled clinical study (GENERATION) on the effect of saxagliptin in elderly patients with type 2 diabetes mellitus not controlled on metformin monotherapy, are being assessed by the EMA.

The final results of the DIAPAZON study with the objective of describing the use of saxagliptin in real life and evaluating the impact on the state of health of patients with type 2 diabetes mellitus in France are expected in July 2015.

A program of 5 pharmacoepidemiological studies respectively intended to evaluate major cardiovascular events, the risk of acute renal impairment or acute hepatic impairment, the risk of infection, the impact on lymphocytes and the risk of severe hypersensitivity, angioedema and other severe cutaneous reactions will be conducted on 4 different databases, 2 of which are in the USA (HIRD and Medicare Part D) and 2 of which are in the UK (GPRD and THIN).

010 THERAPEUTIC USE

In the absence of a direct comparison with validated and available triple therapies, none can be recommended in preference.

Saxagliptin (ONGLYZA) is a therapeutic option which can be used in combination with a sulfonylurea and metformin when diet and exercise plus dual therapy with these medicinal products does not provide adequate glycaemic control.

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 mellitus is a chronic disease with potentially serious complications, particularly cardiovascular complications.
◗ ONGLYZA is used in the context of treatment for hyperglycaemia.
◗ The efficacy/adverse effects ratio is high.
◗ ONGLYZA is a treatment to be used as triple oral therapy in combination with metformin and a sulfonylurea when diet and exercise plus dual therapy with these medicinal products does not provide adequate glycaemic control.
◗ There are treatment alternatives to this proprietary medicinal product.

◗ Public health benefit:
The public health burden which type 2 diabetes mellitus represents is substantial. The burden represented by the sub-population of patients for whom ONGLYZA is indicated (triple therapy) is moderate.
Improving the therapeutic management of type 2 diabetics is a public health need.
The proprietary medicinal product ONGLYZA is not likely to present a public health benefit for this extension of indication as triple oral therapy, given the absence of additional impact on public health criteria (morbidity and mortality data, improved quality of life) compared with the current management of type 2 diabetes mellitus.

Taking account of these points, the Committee considers that the actual benefit of ONGLYZA is substantial in the extension of the MA indication "In combination with metformin and a sulfonylurea when this treatment alone, combined with diet and exercise, does not provide adequate glycaemic control."

The Committee recommends inclusion 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: 65%**

011.2 Improvement in actual benefit (IAB)

In the absence of a direct comparison with validated and available triple therapies, the Transparency Committee considers that ONGLYZA does not provide an improvement in actual benefit (IAB V, non-existent) in the treatment of patients with type 2 diabetes mellitus as triple oral therapy, namely, in combination with metformin and sulfonylurea when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

011.3 Target population

In this extension of the indication, the target population of ONGLYZA corresponds to patients with type 2 diabetes mellitus treated with triple oral therapy, in combination with a sulfonylurea and metformin, when diet and exercise plus dual therapy with these medicinal products does not provide 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 antidiabetics alone, which is 571,000 patients. The number of patients with HbA1c > 7% is estimated to be 50% according to ENTRED data.
The population of patients failing properly conducted metformin and sulfonylurea dual therapy would therefore amount to **285,000 people.**

The target population of ONGLYZA, as triple therapy, in combination with a sulfonylurea and metformin is within this population.

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

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