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TRANSPARENCY COMMITTEE

Opinion
15 May 2013

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: BRISTOL-MYERS SQUIBB

INN	Saxagliptin
ATC Code (2013)	A10BH03 (DPP-4 inhibitors or gliptins)
Reason for the review	Extension of indication
Lists concerned	National Health Insurance (French Social Security Code L.162-17) for the B/30 tablets Hospital use (French Public Health Code L.5123-2) for the B/30 et B/90 tablets
Indication concerned	“ONGLYZA is indicated in adult patients aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control <u>as combination therapy with insulin (with or without metformin)</u> , when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.”

Actual Benefit	<p><u>Insufficient, and provisional pending re-assessment of gliptins in dual therapy, in combination with insulin when this treatment alone, with diet and exercise, does not provide adequate glycaemic control, for reimbursement by national insurance.</u></p> <p><u>Low, and provisional pending re-evaluation of gliptins in triple therapy, in combination with insulin and metformin when this combination alone, with diet and exercise, does not provide adequate glycaemic control.</u></p>
Improvement in Actual Benefit	<p>In dual therapy in combination with insulin: not applicable.</p> <p>In triple therapy in combination with insulin and metformin, ONGLYZA does not offer any improvement in actual benefit (IAB V, non-existent) in the treatment of patients with type 2 diabetes in whom this combination alone, with diet and exercise, does not provide adequate glycaemic control.</p>
Therapeutic use	<p>ONGLYZA has no role in the treatment of patients with type 2 diabetes as dual therapy in combination with insulin.</p> <p>In triple therapy, in view of its weak efficacy and the doubts as to its safety profile, the role of saxagliptin will be defined after the re-assessment of all gliptins.</p>
Recommendations	<p>The Transparency Committee recommends that the follow-up study¹ requested in December 2009 should be extended to patients affected by this extension of indication.</p> <p>The Committee wishes to re-assess all incretins, gliptins and GLP-1 analogues across all their therapeutic indications, taking into account the available data on their safety profile, in particular on pancreatic effects, the degree of effect observed in terms of glycaemic control and their therapeutic use.</p>

¹ This study, requested by the Committee in its opinion of 2 December 2009, should aim “to describe the actual situation with regard to treatment:

- the characteristics of the patients treated (including age, BMI, 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 discontinuations and the reasons for them;
- change in HbA1c value and weight, as well as hypoglycaemia and long-term safety (2 years).”

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (centralised procedure): 1 October 2009 Date of the extension of indication: 22 November 2011
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, excluding insulins A10BH Dipeptidyl peptidase-4 (DPP-4) inhibitors A10BH03 saxagliptin
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02 BACKGROUND

This opinion responds to an application for inclusion of the proprietary medicinal product ONGLYZA 5 mg in a new indication in the treatment of type 2 diabetes, namely as dual therapy in combination with insulin or as triple therapy in combination with insulin and metformin.

Saxagliptin 5 mg obtained European Marketing Authorisation on 1 October 2009 for the treatment of type 2 diabetes in combination with metformin or a sulphonylurea. In its opinion of 2 December 2009, the Committee indicated substantial actual benefit and IAB V for these indications in the treatment of patients with type 2 diabetes in dual oral therapy.

The proprietary medicinal product ONGLYZA 5 mg is included on the list of reimbursable proprietary medicinal products, approved for hospital use and has been marketed in France since 4 September 2010.

In February 2011, Marketing Authorisation was awarded for a lower dose of saxagliptin (2.5 mg) intended as a dose adjustment in patients with moderate to severe renal impairment. In its opinion of 21 September 2011, the Committee accorded ONGLYZA 2.5 mg an insufficient actual benefit. The pharmaceutical company withdrew its application.

In view of the opinions issued on 18 July 2012 by the Transparency Committee regarding the other DPP-4 inhibitors (JANUVIA/XELEVIA, sitagliptin) indicated primarily as dual therapy in combination with insulin and for which the Committee accorded insufficient actual benefit in this indication, the pharmaceutical company Bristol-Myers Squibb is applying for reimbursement solely in the indication as triple therapy in combination with insulin and metformin.

For this extension of indication application, the company has submitted the results of a pivotal study.

03 THERAPEUTIC INDICATIONS

“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 sulphonylurea, when the sulphonylurea 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 (*indication already assessed by the TC* but obsolete, as glitazones are no longer available in France*)
- **as combination therapy with insulin (with or without metformin), when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.**”

* *Indications already evaluated by the TC (see opinion of 2 December 2009)*

04 DOSAGE IN THE NEW INDICATION

“The recommended dose of ONGLYZA is 5 mg once daily in combination with metformin, insulin or a sulphonylurea.

The safety and efficacy of saxagliptin as triple oral therapy in combination with metformin and a thiazolidinedione have not been established.

Special populations

Elderly (≥65 years)

No dose adjustment is recommended based solely on age. Experience in patients aged 75 years and older is very limited and caution should be exercised when treating this population (see sections 4.4, 5.1 and 5.2 of the SPC).

Renal impairment

No dose adjustment is recommended for patients with mild renal impairment. The dose of ONGLYZA should be reduced to 2.5 mg once daily in patients with moderate or severe renal impairment.

The experience in patients with severe renal impairment is very limited. Therefore, saxagliptin should be used with caution in this population. ONGLYZA is not recommended for patients with end-stage renal disease (ESRD) requiring haemodialysis (see section 4.4 of the SPC).

Because the dose of ONGLYZA should be limited to 2.5 mg based upon renal function, assessment of renal function is recommended prior to initiation of ONGLYZA, and, in keeping with routine care, renal assessment should be done periodically thereafter (see sections 4.4 and 5.2 of the SPC).

Hepatic impairment

No dose adjustment is necessary for patients with mild or moderate hepatic impairment. Saxagliptin should be used with caution in patients with moderate hepatic impairment, and is not recommended for use in patients with severe hepatic impairment (see section 4.4 of the SPC).

Paediatric population

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

Method of administration

ONGLYZA can be taken with or without a meal at any time of the day. If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.”

05 THERAPEUTIC NEED

Type 2 diabetes is a chronic and progressive disease with high morbidity and mortality rates resulting from its microvascular and macrovascular complications. Chronic hyperglycaemia is the main pathogenic factor in microvascular complications (retinopathy, nephropathy, neuropathy) and one of the contributing factors to the macrovascular risk (coronary heart disease, peripheral vascular disease).

Treatment aims to control the blood glucose level, i.e. to control HbA1c and the associated risk factors.

The choice of drug therapy and the aims of treatment should be tailored to the individual patient (age, duration of diabetes, particular situations, hypoglycaemic risk, etc.).

Patients with type 2 diabetes are first treated with diet and lifestyle changes (active measures against a sedentary lifestyle and dietary planning) which are essential interventions at all stages of diabetes management.

Oral anti-diabetic drugs are introduced when diet and lifestyle changes are no longer sufficient to control blood glucose levels.

The latest updates of the international guidelines present approaches derived from the results of large trials (VADT, ACCORD, ADVANCE and results from the 10-year UKPDS follow-up survey) and the introduction of incretin mimetics (GLP-1 analogues and DPP-4 inhibitors or gliptins).

The NICE guidelines² define the role of DPP-4 inhibitors in dual or triple therapy and recommend that they are continued only if a significant drop in the HbA1c level (-0.5%) is achieved within 6 months.

The most recent ADA/EASD guidelines³ propose a change to the target HbA1c (7% to reduce the microvascular risk). These guidelines, updated in 2012,⁴ as well as the SIGN guidelines (Scottish Intercollegiate Guidelines Network)⁵ now propose that blood glucose targets are centred on the patient. They define the role of DPP-4 inhibitors in dual therapy as an alternative to sulphonylureas in patients in whom hypoglycaemia or weight gain may pose a problem. They also recognise the change from one dual therapy to another as an alternative to direct escalation.

In patients with high HbA1c levels (> 9.0%), dual therapy from the outset or insulin therapy may be offered as first-line treatment.

Some patients do not reach or do not maintain blood glucose targets on insulin therapy alone. In these cases, it is recommended to combine insulin with another anti-diabetic drug. In practice, it is metformin that is widely used in combination with insulin.³

² National Institute for Clinical Excellence. London: NICE; 2009. Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes. This short clinical guideline partially updates NICE clinical guideline 66. The recommendations have been combined with unchanged recommendations from CG66 in NICE clinical guideline 87. <http://www.nice.org.uk/cg87>

³ Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, *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(1): 17-30.

⁴ Inzucchi S *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 Jun; 35(6): 1364-79.

⁵ Scottish Intercollegiate Guidelines Network SIGN; 2010, Management of diabetes. A national clinical guideline. <http://www.sign.ac.uk/pdf/sign116.pdf>

Where metformin is contraindicated or poorly tolerated, sulphonylureas are offered. If the targets are not met with these dual therapies, the doses of insulin may be increased, but this dose increase is often associated with a higher risk of hypoglycaemia and with weight gain.

Sitagliptin has been evaluated by the Committee as a treatment option that could be added to the insulin/metformin combination (see opinion of 18 July 2012).

In its draft opinion dated 20 March 2013 (currently in the comments stage), the Committee stated that:

- gliptins (including linagliptin, TRAJENTA) have no role in the treatment of patients with type 2 diabetes as dual therapy in combination with insulin;
- linagliptin is a treatment option that could be added to the insulin/metformin combination.

It should be emphasised that this treatment situation (triple therapy in combination with insulin and metformin) has not been not addressed in the good practice guidelines updated by HAS in January 2013 on glycaemic control in type 2 diabetes.

06 CLINICALLY RELEVANT COMPARATORS

The clinically relevant comparators for the medicine evaluated are medicines available at the same stage of the therapeutic strategy and intended for the same population, on the date of the assessment.

In this case, these are the medicines indicated in type 2 diabetes:

- as dual therapy in combination with insulin

- as triple therapy in combination with insulin and metformin

06.1 Medicinal products

INN	Same pharmacotherapeutic class	Name (Company)	Date of opinion	AB	IAB (Wording)	Reimbursed
Biguanides						
Metformin and its generics	No	GLUCOPHAGE (Merck Santé)	21 July 2010 (renewal of inclusion)	Substantial		Yes
Insulin secretagogues						
Sulphonylureas and their generics	No			Substantial		Yes
Alpha-glucosidase inhibitors (acarbose, miglitol)	No	GLUCOR (Bayer Santé) DIASTABOL (Sanofi Aventis)	5 September 2012 (renewal of inclusion)	Substantial		Yes
Parenteral incretin mimetics or GLP-1 analogues						
Exenatide	No	BYETTA (Lilly)	Not assessed by the TC ⁶			
Gliptins						
Sitagliptin and fixed-dose combinations with metformin	Yes	JANUVIA 100 mg/ XELEVIA 100 mg (MSD, Pierre Fabre)	18 July 2012 (extension of indication)	In dual therapy in combination with insulin: insufficient AB	N/A	No
				In triple therapy in combination with insulin and metformin: substantial AB	IAB V	Yes
Vildagliptin and fixed-dose combinations with metformin	Yes	GALVUS / JALRA (Novartis)	Not assessed by the TC ⁷			
Linagliptin	Yes	TRAJENTA (Boehringer Ingelheim)	20 March 2013	In dual therapy in combination with insulin: insufficient AB	N/A	Draft opinion at comments stage
				In triple therapy in combination with insulin and metformin: substantial AB	IAB V	

⁶ BYETTA (exenatide) was approved by the CHMP on 16 February 2012 for the following extension of indication: "BYETTA is also indicated as adjunctive therapy to basal insulin with or without metformin and/or pioglitazone in adults who have not achieved adequate glycaemic control with these agents."

⁷ Vildagliptin-based proprietary medicinal products received CHMP approval on 20 September 2012 for the following extension of indication: "in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control".

06.2 Other health technologies

Not applicable.

► Conclusion

Metformin and sulphonylureas are the clinically relevant comparators in dual therapy in combination with insulin.

In triple therapy in combination with insulin and metformin, the comparators with Marketing Authorisation are GLP-1 analogues and gliptins. These cannot be considered as relevant.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSEMENT	
	YES / NO If not, why not	Population(s) MA population or restricted
USA	Yes	All indications are eligible for reimbursement
Russia	Yes	All indications are eligible for reimbursement
Brazil	Yes	All indications are eligible for reimbursement
Spain, Italy, Germany	Yes	All indications are eligible for reimbursement
UK	Yes	As 2 nd line treatment when sulphonylureas are contraindicated

08 ANALYSIS OF AVAILABLE DATA

The company has submitted a randomised, double-blind pivotal trial in support of its application (study CV181057⁸), evaluating saxagliptin versus placebo in combination with insulin therapy, with or without metformin, in patients with poorly controlled diabetes on insulin alone or insulin combined with metformin.

08.1 Efficacy

8.1.1 Study CV181057: in combination with insulin, with or without metformin

Aim and method: A phase III, 2:1 randomised, double-blind trial aiming to compare the efficacy and safety of combined insulin + saxagliptin with combined insulin + placebo (with or without metformin) after 24 weeks of treatment.

The study also included a 28-week double-blind extension phase.

The aims of this long-term follow-up period were to evaluate safety and changes between baseline and 52 weeks in HbA1c level, daily dose of insulin administered, percentage of patients with an

⁸ Barnett AH, Charbonnel B, Donovan M et al. Effect of saxagliptin as add-on therapy in patients with poorly controlled type 2 diabetes on insulin alone or insulin combined with metformin. *Curr Med Res Opin.* 2012 Apr; 28(4): 513-23.

HbA1c level < 7% and weight. As this phase had an exploratory design (multiple endpoints, no statistical tests performed), it is for information only and no conclusions can be drawn from it.

The protocol provided for stratified randomisation according to whether treatment was combined with metformin or not.

Inclusion criteria:

Patients with type 2 diabetes, poorly controlled (HbA1c level $\geq 7.5\%$ and $\leq 11\%$) by insulin therapy (with intermediate-acting or long-acting or mixed insulin at a stable dose ≥ 30 IU/day and ≤ 150 IU/day), possibly combined with a stable dose of metformin for at least 8 weeks.

Exclusion criteria: other anti-diabetic treatments in the past 8 weeks, cardiovascular history (myocardial infarction, CVA, transient ischaemic attack, NYHA class III or IV congestive heart failure, left ventricular ejection fraction < 40%) in the past 6 months, contraindications to metformin.⁹

Dosing regimen:

Four hundred and fifty-five (455) patients were randomised to receive:

- either combined insulin + saxagliptin 5 mg/day \pm metformin (n=304)
- or combined insulin + placebo \pm metformin (n=151).

During the first 24 weeks of treatment, the doses of insulin and metformin prescribed at the time of randomisation had to remain stable. Nonetheless, the protocol allowed for an increase or decrease in insulin dose by a maximum of 20% during this phase. Between weeks 24 and 52, changes to insulin dose and to the type of insulin were authorised.

All patients had to pursue the recommended dietary and physical exercise programme throughout the study.

Primary efficacy endpoint:

Average change in HbA1c level after 24 weeks of treatment compared with the baseline value.

The protocol envisaged the inclusion of 390 patients (260 in the saxagliptin group and 145 in the placebo group) in order to demonstrate a difference of 0.35% in the change in HbA1c level with a power of 90% and an overall significance level of 0.05.

Analyses for the primary efficacy endpoint specified in the protocol were performed in subgroups of patients (based on whether or not insulin treatment was combined with metformin, the initial HbA1c level, BMI, and the duration of diabetes). As no adjustment method was applied to take account of multiple comparisons, the possibility of an overestimation of the effect cannot be ruled out. Consequently, no conclusions can be drawn on the basis of these exploratory analyses, and they are therefore not presented.

Main secondary endpoints after 24 weeks of treatment:

- mean change in the fasting blood glucose level (FBG)
- percentage of patients with an HbA1c level < 7%
- mean daily dose of insulin administered.

Other endpoints:

Use of a rescue therapy.¹⁰

⁹ Main contraindications to metformin: renal failure

¹⁰ Any change in the dose and/or type of insulin, or withdrawal from the trial due to insufficient glycaemic control, was considered to be a rescue therapy.

Results:

The results were obtained from analysis of all patients who were randomised and received at least one dose of treatment.

On inclusion, the characteristics of the patients in the two treatment groups were similar. They were:

- aged 57.2 on average (77% of patients were under 65);
- in most cases obese (mean BMI of about 32.3 kg/m²).

The majority of the patients had been diagnosed with diabetes more than 5 years ago.

The mean HbA1c level on inclusion was 8.66 ± 0.88%. The majority of the patients (about 40%) had an HbA1c level between 8 and 9%. 25.1% of patients had an HbA1c level below 8% and 33% of patients had an HbA1c level ≥ 9%. It should be noted that HbA1c levels on inclusion were high.

The type of insulin used to treat patients was:

- mixed in the majority of cases (59.9% in the saxagliptin group and 50.3% in the placebo group),
- intermediate-acting (17.8% and 21.2% respectively),
- or long-acting (17.1% and 19.2% respectively).

The mean dose of insulin was 54.2 U/day across all patients randomised. The mean dose of metformin taken was 1,805 mg in the saxagliptin group and 1,861 mg in the placebo group. It was administered in 69% of patients (314/455).

Table 1: Characteristics of the patients included

	Placebo group N=151	Saxagliptin group N=304	Total N=455
Mean age (standard deviation SD)	57.3 (9.27)	57.2 (9.43)	57.2 (9.37)
Age N (%)			
< 65 years	118 (78.1)	233 (76.6)	351 (77.1)
≥ 65 years	33 (21.9)	71 (23.4)	104 (22.9)
≥ 75 years	3 (2.0)	6 (2.0)	9 (2.0)
Mean BMI on inclusion (kg/m²) (SD)	31.76 (4.76)	32.57 (5.65)	32.30 (5.38)
BMI on inclusion N (%)			
< 30 kg/m ²	61 (40.4)	108 (35.5)	169 (37.1)
≥ 30 kg/m ²	90 (59.6)	196 (64.5)	286 (62.9)
Mean baseline HbA1c values (SD)	8.64 (0.86)	8.67 (0.90)	8.66 (0.88)
Baseline HbA1c values (category) [N (%)]			
< 8%	38 (25.2)	76 (25.0)	114 (25.1)
≥ 8% and < 9%	65 (43.0)	126 (41.4)	191 (42.0)
≥ 9%	48 (31.8)	102 (33.6)	150 (33.0)
Time since diabetes diagnosis N (%)			
Mean duration (SD)	12.2 (7.37)	11.8 (6.93)	12.0 (7.07)
≥ 5 years	127 (84.1)	258 (84.9)	385 (84.6)
≥ 10 years	94 (62.3)	169 (55.6)	263 (57.8)
Mean baseline FBG [mg/dL] (SD)*	173.1 (55.8)	173.5 (54.3)	173.4 (54.7)

* values available in 453 patients (placebo group n = 150, saxagliptin group n = 303)

Primary efficacy endpoint:

Table 2: Change in HbA1c levels after 24 weeks:

Treatment groups	N	Mean initial HbA1c level (standard deviation)	Adjusted mean change in HbA1c levels (SD)	Difference/mean comparator, 95% CI, p
insulin + placebo ± metformin	149	8.66 (0.07)	-0.32 (0.07)	
insulin + saxagliptin ± metformin	300	8.67 (0.05)	-0.73 (0.05)	- 0.41 [-0.59; -0.24] p < 0.0001

After 24 weeks of treatment, the reduction in HbA1c was greater among patients taking insulin + saxagliptin ± metformin than among those taking insulin + placebo ± metformin (difference between saxagliptin and placebo: -0.41%, 95% CI [-0.59; -0.24]; p < 0.0001).

It should be noted that saxagliptin was most effective up to the 12th week of treatment. HbA1c levels rose slightly after that point.

Secondary endpoints:

➤ mean change in the fasting blood glucose level (FBG)

No difference was observed between the two treatment groups.

➤ percentage of patients with an HbA1c level < 7%

The treatment target on insulin therapy was achieved by 17.3% of patients analysed from the saxagliptin group (52/300) and 6.7% of patients from the placebo group (10/149).

➤ mean daily dose of insulin administered

The mean dose of insulin administered was 55.1 U/day in the saxagliptin group and 60.3 U/day in the placebo group.

Other criteria: use of a rescue therapy

The percentage of patients needing a rescue therapy at least once was 31.8% in the placebo group and 22.7% in the saxagliptin group.

Follow-up data at 52 weeks

Of the 455 patients initially included, 402 (88.4%) participated in the extension phase (268 patients from the saxagliptin group, 88.2%; 134 patients from the placebo group, 88.7%) and 371 completed the 52-week follow-up, comprising 246 patients from the saxagliptin group (80.9%) and 125 patients from the placebo group (82.8%).¹¹

After 52 weeks of treatment, the reduction in HbA1c levels was -0.70±0.07% in the saxagliptin group (n=244) and -0.36±0.09% in the placebo group (n=124), with a between-group difference of -0.34, 95% CI [-0.56; -0.13], p not calculated.

The treatment target (HbA1c level < 7%) was achieved by 21.3% of patients (n = 64) on saxagliptin and 8.7% of patients on placebo (n=13).

¹¹ It should be noted that the most common reasons for withdrawal from the trial during the 52 weeks were withdrawal of patient consent (17 patients in the saxagliptin group and 7 in the placebo group) and the occurrence of an adverse event (10 patients on saxagliptin, 3 on placebo).

08.2 Safety/Adverse effects

8.2.1 Data obtained from study CV181057

There was at least one adverse event in 71.5% of the patients on placebo (108/151) and 66.4% of the patients on saxagliptin (202/304).

The main adverse events observed were:

- hypoglycaemia in 26.5% of patients on placebo and 22.7% of patients in the saxagliptin group
- infections (primarily nasopharyngitis, urinary tract infections and upper respiratory tract infections) in 41.1% of patients on placebo and 35.5% of patients on saxagliptin
- skin and subcutaneous tissue disorders, primarily allergic dermatitis, skin ulcer, urticaria and rash, in 8 patients on placebo and 15 on saxagliptin
- cardiovascular events (myocardial infarction, acute coronary syndrome, unstable angina, transient ischaemic attack) in two patients in the placebo group and four patients in the saxagliptin group

These events were treatment-related in 22.5% of the patients on placebo (i.e. 34 patients) and 18.4% of the patients on saxagliptin (56 patients). The most common event attributable to treatment was mild to moderate hypoglycaemia in 22 patients on placebo and 31 on saxagliptin. Serious adverse events were observed in a total of 38 patients (13 on placebo and 25 on saxagliptin).

The following gliptin-specific events were observed:

- hypersensitivity reactions (urticaria) in one patient on placebo and three on saxagliptin
- fractures in three patients from each group
- pancreatitis in one patient on placebo

No difference in change in weight was observed between the placebo and saxagliptin groups at 24 and 52 weeks of treatment.

Treatment was discontinued because of an adverse event in three patients from the placebo group and nine from the saxagliptin group.

8.2.2 SPC data

“In post-marketing experience with saxagliptin there have been spontaneously reported adverse reactions of acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of saxagliptin. If pancreatitis is suspected, ONGLYZA and other potentially suspect medicinal products should be discontinued.

During post-marketing experience, including spontaneous reports and clinical trials, the following adverse reactions have been reported with the use of saxagliptin: serious hypersensitivity reactions, including anaphylactic reaction, anaphylactic shock, and angioedema.

Although skin lesions were not observed at an increased incidence in clinical trials, there is limited experience in patients with diabetic skin complications. Post-marketing reports of rash have been described in the DPP-4 inhibitor class. Rash is also noted as an adverse event for ONGLYZA. Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering, ulceration or rash, is recommended.”

The SPC states that saxagliptin is contraindicated in patients with a history of a serious hypersensitivity reaction, including anaphylactic reactions, anaphylactic shock and angioedema, to saxagliptin or any other DPP-4 inhibitor.

8.2.3 Data from the first six PSURs (periods from 31 July 2009 to 30 July 2012)

Analysis of the most recent PSUR (period from 21 January 2012 to 30 July 2012) identified 31 cases of pruritus, 26 cases of rash, 13 cases of urticaria, 28 cases of pancreatitis and 23 cases of abdominal pain.¹²

An analysis of the first 6 PSURs focusing specifically on the occurrence of hypersensitivity reactions and pancreatitis is available. During this period:

- regarding hypersensitivity reactions:

- 93 serious cases were identified including 25 cases of angioedema, 16 cases of urticaria, 9 cases of hypersensitivity, 7 anaphylactic reactions and 5 cases of anaphylactic shock;
- 94 non-serious cases including 44 cases of urticaria and 26 cases of hypersensitivity were noted.
- In the ongoing morbidity-mortality study (SAVOR), 22 events have been recorded.
- None of these cases have required hospitalisation or been life-threatening.

- regarding pancreatitis:

- 113 serious cases including 80 cases of pancreatitis, 31 of acute pancreatitis and 2 of chronic pancreatitis were noted.
- In the SAVOR study, to date there have been 37 cases of pancreatitis, 10 cases of acute pancreatitis and 4 of chronic pancreatitis.

The SPC and RMP have been updated to include the following identified risks: pancreatitis, severe hypersensitivity reactions (anaphylactic reactions, angioedema), gastrointestinal disorders (including nausea), dermatitis and pruritus.

The potential risks are: skin lesions in the form of skin ulcers, erosion and necrosis; lymphopenia; thrombocytopenia; hypoglycaemia; opportunistic infections; fractures; and severe skin reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome.

08.3 Summary & discussion

Saxagliptin in combination with insulin therapy, with or without metformin, in type 2 diabetes has been evaluated in a 2:1 randomised, double-blind, placebo-controlled trial in 455 poorly controlled, mostly obese patients with a mean age of 57 years who were treated for 24 weeks. This study included a 28-week double-blind follow-up phase.

The mean HbA1c level on inclusion was $8.7 \pm 0.9\%$.

After 24 weeks of treatment, the reduction in HbA1c was greater with insulin + saxagliptin \pm metformin than with insulin + placebo \pm metformin (difference between saxagliptin and placebo: -0.41% , 95% CI $[-0.59; -0.24]$; $p < 0.0001$).

The effect of saxagliptin on HbA1c levels was greatest up to the 12th week of treatment, then it diminished.

The results of the long-term follow-up at 52 weeks are exploratory and therefore the level of evidence is insufficient to draw any conclusions.

¹² For sitagliptin (JANUVIA - PSUR from 4 August 2009 to 3 August 2011), the most commonly reported cases were: gastrointestinal disorders, with a total of 1,933 reports including 2,488 events, primarily pancreatitis (459 events), acute pancreatitis (133), nausea (268) and diarrhoea (244); skin and subcutaneous tissue disorders with 1,190 events, primarily rash (317 cases), pruritus (178 cases) and urticaria (105 cases); and metabolism and nutrition disorders with 850 events including hypoglycaemia (628 events), decreased appetite (78 events) and hyperglycaemia (38 events).

For linagliptin (TRAJENTA), analysis of the first two PSURs (from 2 May 2011 to 2 May 2012) revealed 29 cases of pancreatitis and 3 cases of hypersensitivity.

The responder rate was low, with the treatment target on insulin therapy after 24 weeks only being achieved by 17.3% of patients in the saxagliptin group (52/300) and 6.7% of patients in the placebo group (10/149).

The majority of patients (70%) were on triple insulin / metformin / saxagliptin therapy, and data that would allow dual insulin / saxagliptin therapy to be evaluated are limited. A comparison group with an optimised insulin regimen would have been useful to discern the benefit of adding saxagliptin.

The EPAR states that treatment was discontinued due to poor glycaemic control in 22.7% of patients in the saxagliptin group and 32.8% in the placebo group.¹³ Almost a third of patients in each group needed a rescue treatment.

Overall, the effect of saxagliptin is similar to the degree of effect observed within its class, but appears weaker.

This effect, primarily evaluated in triple therapy in combination with insulin and metformin, is modest in terms of the reduction in HbA1c levels compared with existing alternatives¹⁴ and smaller than those observed with other gliptins.^{15, 16, 17, 18} The authors of a meta-analysis of 29 trials evaluating the efficacy and safety of incretin mimetics concluded that their efficacy was modest (reduction in HbA1c value compared with placebo of -0.74%, 95% CI [-0.85; -0.62] for the gliptins, non-inferiority compared with active comparators).

No study has shown that saxagliptin is superior in its Marketing Authorisation indications to a reference treatment.¹⁹

There are no morbidity and mortality data but a study is underway.

In this study, the main adverse events were hypoglycaemia (22.7% with saxagliptin versus 26.5% with placebo) and infections, primarily upper respiratory tract and urinary tract infections (35.5% versus 41.1%). The following were more common in the saxagliptin group than in the placebo group: treatment discontinuation due to an adverse event (9 patients versus 3), severe adverse events (25 versus 13), hypoglycaemia attributable to treatment (31 versus 22), cardiovascular events (4 versus 2), skin events (15 versus 8), and hypersensitivity reactions (3 versus 1). Change in weight at 24 and 52 weeks was no different between placebo and saxagliptin.

Analysis of the first six PSURs revealed 187 hypersensitivity reactions (of which 93 cases were serious, including 25 cases of angioedema, 16 cases of urticaria, 9 cases of hypersensitivity, 7 anaphylactic reactions and 5 cases of anaphylactic shock) and 113 serious cases of pancreatitis (comprising 80 cases of pancreatitis, 31 of acute pancreatitis and 2 of chronic pancreatitis).

¹³ EMA. Assessment report of saxagliptin - EPAR. 20 October 2011

¹⁴ The mean changes in HbA1c values observed were:

- -1 to -1.5% with metformin
- -1 to -1.5% with sulphonylureas
- -0.8% with glinides
- -0.5 to 1% with alpha-glucosidase inhibitors

¹⁵ Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. Renee E. Amori et al. JAMA 2007; 298 (2): 194-206.

¹⁶ Richter B. et al. Dipeptidyl peptidase-4 inhibitors for type 2 diabetes mellitus. The Cochrane Database of Systematic Reviews 2008, Issue 2.

¹⁷ Don Dicker et al. DPP-4 inhibitors. Impact on glycaemic control and cardiovascular risk factors. Diabetes Care, Vol 34, Supplement 2, May 2011.

¹⁸ After 24 weeks of treatment, the reduction in HbA1c levels (primary efficacy endpoint) was greater among patients taking insulin + sitagliptin ± metformin than among those taking insulin + placebo ± metformin (difference between sitagliptin and placebo: -0.56%, 95% CI [-0.70; -0.42]; p < 0.001) in a study including 641 patients. This reduction is of a similar size in the strata of patients taking and not taking metformin (see TC opinions on JANUVIA / JANUMET / XELEVIA / VELMETIA dated 18 July 2012).

After 24 weeks of treatment, the reduction in HbA1c was greater with insulin + linagliptin ± OAD (metformin for 75% of patients) than with insulin + placebo ± OAD (difference between linagliptin and placebo: -0.65%, 95% CI [-0.74; -0.55]; p < 0.0001) in a study including 1,261 patients.

¹⁹ T. Karagiannis et al. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. BMJ. 2012 Mar 12;344:e1369. doi: 10.1136/bmj.e1369.

The European RMP, in addition to standard pharmacovigilance, includes monitoring of the following risks: hypoglycaemia (particularly in association with a sulphonylurea), gastrointestinal disorders, pancreatitis, and hypersensitivity reactions, angioedema and urticaria. The potential risks identified are skin lesions, severe hypersensitivity reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome), infections and the risk of bone fracture.

One study,²⁰ conducted by an independent group of academic researchers, suggests an increased risk of pancreatitis and of precancerous cell changes (known as pancreatic duct metaplasia) in patients with type 2 diabetes treated with incretins (GLP-1 analogues and DPP-4 inhibitors). The results of this study are currently being evaluated by the European health authorities. In parallel, the FDA is investigating an increased risk of pancreatitis and precancerous changes due to incretins.

08.4 Programme of studies

The following studies are currently underway:

- the SAVOR study, a phase IV, randomised, double-blind, placebo-controlled trial, will evaluate the effect of saxagliptin on the incidence of cardiovascular events in 16,500 patients with type 2 diabetes followed up for 5 years;
- the GENERATION study, a phase IIIb/IV, randomised, controlled, double-blind trial versus glimepiride, will evaluate the effect of saxagliptin in elderly patients with poorly controlled type 2 diabetes on metformin monotherapy;
- the DIAPAZON study aims to describe real-life use of saxagliptin and to evaluate its impact on the health status of patients with type 2 diabetes in France;
- a programme of five pharmacoepidemiological studies, designed to evaluate major cardiovascular events, the risk of acute kidney injury or acute liver failure, the risk of infection, the effect on lymphocytes, and the risk of severe hypersensitivity, angioedema and other severe skin reactions respectively, will be conducted on four different databases, comprising two in the USA (HIRD and Medicare Part D) and two in the UK (GPRD and THIN).

09 THERAPEUTIC USE

Gliptins (including saxagliptin) have no role in the treatment of patients with type 2 diabetes as dual therapy in combination with insulin.

In triple therapy, the role of saxagliptin, in view of its weak efficacy and the doubts as to its safety profile, will be defined after the re-assessment of all gliptins.

It should be emphasised that this treatment situation (triple therapy in combination with insulin and metformin) has not been addressed in the good practice guidelines updated by HAS in January 2013 on glycaemic control in type 2 diabetes and that its clinical relevance is questionable.

²⁰ The study was performed by examining a small number of pancreatic tissue samples from organ donors with and without diabetes and whose death resulted from a cause other than diabetes.

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

010.1 Actual benefit

10.1.1 In dual therapy in combination with insulin

Type 2 diabetes is a chronic disease with potentially serious complications, particularly cardiovascular complications.

ONGLYZA is a treatment for hyperglycaemia.

In view of:

- the lack of clinical practice recommendations for this dual therapy and the fact that the only anti-diabetic drugs recommended in combination with insulin and used in practice are metformin and sulphonylureas;
 - the lack of any trial comparing combined insulin + saxagliptin versus insulin + metformin or versus insulin + sulphonylurea which would allow the benefit and contribution of this dual therapy to be quantified;
 - the low number of patients treated with insulin alone (30%) in the trial comparing saxagliptin to placebo in combination with insulin;
 - the long-term risks, particularly in relation to cardiac, hepatic, pancreatic and cutaneous adverse events and hypersensitivity reactions, which are poorly defined;
- the efficacy/adverse effects ratio for ONGLYZA in dual therapy in combination with insulin cannot be qualified.

In view of the available data, this proprietary medicinal product cannot be recommended as dual therapy in combination with insulin. Indeed, where insulin treatment is established, metformin is the standard treatment to use in combination. In a systematic review²¹ including 23 studies and a total of 2,117 patients and evaluating metformin combined with insulin versus insulin alone, the insulin + metformin combination was associated with a greater reduction in HbA1c levels compared with insulin alone (inter-group difference -0.60%, 95% CI [-0.89; -0.31], $p < 0.001$) and with weight gain (+ 1 kg). According to the guidelines,^{3,5} when insulin therapy is started to maintain or improve glycaemic control, dual therapy with insulin + metformin or insulin + sulphonylurea are the validated combinations.

Public health benefit:

The public health burden of type 2 diabetes is substantial because of its high prevalence, which is constantly increasing, and the concomitant microvascular and macrovascular complications. The public health burden in the sub-population of patients with an indication for ONGLYZA in dual therapy is considered to be moderate.

Improvement in the treatment of patients with type 2 diabetes is a public health need which comes within the framework of established priorities.²²

In view of the results of the placebo-controlled clinical trial on glycaemic control alone, it is not anticipated that the proprietary medicinal product ONGLYZA will have any impact on morbidity and mortality or on quality of life in patients treated, in comparison with the currently available dual therapies.

²¹ Hemmingsen B, Christensen LL, Wetterslev J, Vaag A, Gluud C, Lund SS, Almdal T. Comparison of metformin and insulin versus insulin alone for type 2 diabetes: systematic review of randomised clinical trials with meta-analyses and trial sequential analyses. *BMJ*. 2012 Apr 19;344:e1771. doi: 10.1136/bmj.e1771.

²² 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 chronic diseases 2007-2011.

In addition, it is unclear whether the experimental data can be transposed into clinical practice because of uncertainties about the long-term effect of this treatment including its effect on glycaemic control.

In the current state of knowledge, it cannot be presumed that ONGLYZA will offer any response to the identified public health need.

Consequently, no public health benefit is anticipated for the proprietary medicinal product ONGLYZA.

Taking account of these points, the Committee considers that the actual benefit of ONGLYZA as dual therapy, in combination with insulin when this treatment alone, with diet and exercise, does not provide adequate glycaemic control, is insufficient, and provisional pending the re-assessment of gliptins, for reimbursement by National Health Insurance.

10.1.2 In triple therapy in combination with insulin and metformin

Type 2 diabetes is a chronic disease with potentially serious complications, particularly cardiovascular complications.

ONGLYZA is a treatment for hyperglycaemia.

The degree of effect observed in the study in terms of reduction in HbA1c levels is modest and lower than that observed for the two other gliptins evaluated by the Committee in studies with a similar methodology. In addition, the long-term risks, particularly in relation to cardiac, hepatic, pancreatic and cutaneous adverse events and hypersensitivity reactions, are poorly defined and investigations into the increased pancreatic risk are currently being conducted by the American and European authorities.^{20,23} Therefore, the efficacy/adverse effects ratio for this proprietary medicinal product is low.

The role of saxagliptin, in view of its weak efficacy and safety profile, will be defined after the re-evaluation of all gliptins.

Alternative medicinal products exist to this proprietary medicinal product.

Public health benefit:

The public health burden of type 2 diabetes is substantial because of its high prevalence, which is constantly increasing, and the concomitant microvascular and macrovascular complications. The public health burden in the sub-population of patients with an indication for ONGLYZA in triple therapy is considered to be moderate.

Improvement in the treatment of patients with type 2 diabetes is a public health need which comes within the framework of established priorities.²²

In view of the results of the placebo-controlled clinical trial on glycaemic control alone, it is not anticipated that the proprietary medicinal product ONGLYZA will have any impact on morbidity and mortality or on quality of life in patients treated, in comparison with the currently available triple therapies.

In addition, it is unclear whether the experimental data can be transposed into clinical practice because of uncertainties about the long-term effect of this treatment, including its effect on glycaemic control.

In the current state of knowledge, it cannot be presumed that ONGLYZA will offer any response to the identified public health need.

Consequently, no public health benefit is anticipated for the proprietary medicinal product ONGLYZA.

Taking account of these points, the Committee considers that the actual benefit of ONGLYZA as triple therapy in combination with insulin and metformin, when this combination alone, with diet and exercise, does not provide adequate glycaemic control, is low and provisional pending the re-assessment of gliptins.

²³ Deborah Cohen. Reports of pancreatitis are 20-30 times more likely with GLP-1 drugs, analysis finds. News BMJ 2013;346:f2607

➤ **In dual therapy in combination with insulin:**

The Transparency Committee does not recommend inclusion 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.

➤ **In triple therapy in combination with insulin and metformin:**

The Transparency Committee recommends inclusion of the proprietary medicinal product ONGLYZA on the list of medicines refundable by National Health Insurance (B/30) and on the list of medicines approved for use by hospitals and various public services (B/30 and B/90) in the indication cited above and at the dosage in the Marketing Authorisation, pending the re-assessment of gliptins.

010.2 Improvement in actual benefit (IAB)

➤ **In dual therapy in combination with insulin:** not applicable.

➤ **In triple therapy in combination with insulin and metformin:**

In triple therapy in combination with insulin and metformin, ONGLYZA does not offer any improvement in actual benefit (IAB V, non-existent) in the treatment of patients with type 2 diabetes in whom this combination alone, with diet and exercise, does not provide adequate glycaemic control.

010.3 Target population

The target population of ONGLYZA in triple therapy corresponds to patients with type 2 diabetes that is poorly controlled (HbA1c > 7%) by a combination of insulin and metformin.

The prevalence of diabetes treated with drug therapy in France has been estimated by Health Insurance to be 4.4% in 2009,²⁴ that is 2.9 million people. The annual rate of increase is estimated to be 4.7% (rate calculated from general scheme data alone).

In view of the 2009 prevalence and its progression, and assuming that the progression rate is stable in the absence of any updated data, the prevalence of treated diabetes would be almost 3.02 million people in 2012.

The 2007-2010 data from the ENTRED study also provide further details.^{25,26,27}

91.9% of diabetic patients are said to have type 2 diabetes, that is about 2.78 million people.

²⁴ Ricci P, Blotière PO, Weill A, Simon D, Tuppin P, Ricordeau P, Allemand H. Diabète traité : quelles évolutions entre 2000 et 2009 en France ? *BEH* 2010 ; 42-43 : 425-31

²⁵ Echantillon national témoin représentatif des personnes diabétiques (Entred) 2007-2010 Diaporama : Caractéristiques des personnes diabétiques, risque vasculaire, complications et prise en charge médicale (updated on 12 March 2010). http://www.invs.sante.fr/surveillance/diabete/entred_2007_2010/resultats_metropole_principaux.htm

²⁶ Fagot-Campagna A, Fosse S, Roudier C, Romon I, Penfornis A, Lecomte P, Bourdel-Marchasson I, Chantry M, Deligne J, Fournier C, Poutignat N, Weill A, Paumier A, Eschwège E, for the ENTRED Scientific Committee. Caractéristiques, risque vasculaire et complications chez les personnes diabétiques en France métropolitaine : d'importantes évolutions entre Entred 2001 et Entred 2007. *BEH*. 2009 ; 42-43 : 450-455

²⁷ Fagot-Campagna A, Romon I et al (Institut de veille sanitaire) Prévalence et incidence du diabète, et mortalité liée au diabète en France http://www.invs.sante.fr/publications/2010/plaquette_diabete/plaquette_diabete.pdf

➤ Population for the indication in combination with insulin + metformin:

Population under consideration	Numbers under consideration	Comments	Source
Patients treated with insulin in 2007 (23% of type 2 diabetics in 2007)	358 000		TC Opinion on LANTUS (2009)
- On insulin alone (39.0%) - On insulin + OAD (61.0%)	139 620 218 380	14.1% of patients with type 2 diabetes are treated with insulin, of whom 5.5% take insulin alone	ECODIA 2 study, March 2007
<u>Subpopulation on insulin + OAD</u> - 51.5% with HbA1c > 7%	218 380 <u>112 465</u>		ECODIA 2 study, March 2007
Total target population for this indication	<u>112 465 patients</u>		

In total, the target population of ONGLYZA for the extension of the indication as triple therapy in combination with insulin and metformin is estimated to be a maximum of 113,000 patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

► Packaging

Appropriate for the prescription conditions.

► Request for data

The Transparency Committee recommends that the follow-up study¹ requested in December 2009 should be extended to patients affected by this extension of indication.