HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

2 December 2009

VICTOZA 6 mg/ml solution for injection in pre-filled pen
Pack size of two 3 ml pens (CIP: 396 323-6)

Applicant : NOVO NORDISK PHARMACEUTIQUE SAS

liraglutide

ATC Code: A10BX07

List I

Date of MA (centralised procedure): June 30, 2009

Reason for request: inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

liraglutide

1.2. Indications

"VICTOZA is indicated in the treatment of type 2 diabetes in adults to achieve glycaemic control:

- in combination with metformin or a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformine or sulphonylurea.
- in combination with metformin and a sulphonylurea or metformin and a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy."

1.3. Dosage

To improve gastro-intestinal tolerability, the starting dose is 0.6 mg liraglutide daily. After at least one week, the dose should be increased to 1.2 mg. Some patients are expected to benefit from an increase in dose from 1.2 mg to 1.8 mg and based on clinical response, after at least one week the dose can be increased to 1.8 mg to further improve glycaemic control. Daily doses higher than 1.8 mg are not recommended.

Victoza can be added to existing metformin or to a combination of metformin and thiazolidinedione therapy. The current dose of metformin and thiazolidinedione can be continued unchanged.

Victoza can be added to existing sulphonylurea or to a combination of metformin and sulphonylurea therapy. When Victoza is added to sulphonylurea therapy, a reduction in the dose of sulphonylurea should be considered to reduce the risk of hypoglycaemia

Self-monitoring of blood glucose is not needed in order to adjust the dose of Victoza. However, when initiating treatment with Victoza in combination with a sulphonylurea, blood glucose self-monitoring may become necessary to adjust the dose of the sulphonylurea.

Specific populations

Elderly (>65 years old): No dose adjustment is required based on age. Therapeutic experience in patients 75 years of age is limited.

Renal impairment: No dose adjustment is required for patients with mild renal impairment (creatinine clearance ≤60-90 ml/min). There is very limited therapeutic experience in patients with moderate renal impairment (creatinine clearance of 30-59 ml/min) and no therapeutic experience in patients with severe renal impairment (creatinine clearance below 30 ml/min). Victoza can currently not be recommended for use in patients with moderate and severe renal impairment including patients with end-stage renal disease.

Hepatic impairment: The therapeutic experience in patients with all degrees of hepatic impairment is currently too limited to recommend the use in patients with mild, moderate or severe hepatic impairment.

Paediatric population: Victoza is not recommended for use in children below 18 years of age due to lack of data on its safety and efficacy.

Method of administration
Victoza should not be administered intravenously or intramuscularly.
Victoza is administered once daily at any time, independent of meals, and can be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site and timing can be changed without dose adjustment. However, it is preferable that Victoza is injected around the same time of the day, when the most convenient time of the day has been chosen. [1]

1.4. Primary warnings and special precautions for use (see SPC)

There is limited experience in patients with congestive heart failure New York Heart Association (NYHA) class I-II. There is no experience in patients with congestive heart failure NYHA class III-IV.
There is limited experience in patients with inflammatory bowel disease and diabetic gastroparesis and Victoza is therefore not recommended in these patients. The use of Victoza is associated with transient gastrointestinal adverse reactions, including nausea, vomiting and diarrhoea.

Use of other GLP-1 analogues has been associated with the risk of pancreatitis. There have been few reported events of acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, Victoza and other potentially suspect medicinal products should be discontinued.

Thyroid adverse events, including increased blood calcitonin, goitre and thyroid neoplasm have been reported in clinical trials in particular in patients with pre-existing thyroid disease.

Patients receiving Victoza in combination with a sulphonylurea may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by a reduction in the dose of sulphonylurea.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

A: Alimentary tract and metabolism
A10: Drugs used in diabetes
A10B: Blood glucose lowering drugs, excl. insulins
A10BX: Other blood glucose lowering drugs, excl. insulins
A10BX07: liraglutide

2.2. Medicines in the same therapeutic category: GLP-1 analogue

BYETTA 5 µg and 10 µg solution for injection in pre-filled pen (exenatide).
Byetta is indicated for treatment of type-2 diabetes mellitus in combination with metformin and/or a sulphonylurea in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.

NB: the indications of VICTOZA and BYETTA are not entirely identical. BYETTA is not indicated in triple therapy combined with metformin and glitazone.

[1] the dosage of BYETTA is as follows:
BYETTA therapy should be initiated at 5 µg exenatide per dose administered twice daily (BID) for at least one month in order to improve tolerability. The dose of exenatide can then be increased to 10 µg BID to further improve glycaemic control. BYETTA can be administered at any time within the 60-minute period before the morning and
evening meal (or two main meals of the day, approximately 6 hours or more apart). BYETTA should not be administered after a meal.

2.3. Medicines with a similar therapeutic aim

- <u>in dual therapy, in combination with metformin</u>:
  - sulphonylureas
  - glitazones
  - intestinal alpha-glucosidase inhibitors
  - glinides
  - DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin)

- <u>in dual therapy, in combination with a sulphonylurea</u>:
  - glitazones
  - intestinal alpha-glucosidase inhibitors
  - DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin)

<u>- in triple therapy, in combination with metformin and a sulphonylurea</u>:
  - glitazones
  - Insulin
  - DPP-4 inhibitors (sitagliptin)

<u>- in triple therapy, in combination with metformin and a glitazone:</u>
  - sulphonylureas

3. ANALYSIS OF AVAILABLE DATA

The LEAD (Liraglutide Effects and Actions in Diabetes) clinical development programme is based on 6 studies:

- LEAD 1[2] and LEAD 2[3] assessing the efficacy and safety of liraglutide in dual therapy in combination with metformin or a sulphonylurea, glimepiride
- LEAD 3 assessing liraglutide in single therapy (use not recommended in the MA)
- LEAD 4[4] and LEAD 5[5] assessing the efficacy and safety of liraglutide in triple therapy in combination with metformin + glimepiride or in combination with metformin + rosiglitazone
- LEAD 6[6] comparing the efficacy and safety of liraglutide to that of exenatide in dual or triple therapy.

In all the studies, there were many comparisons (see hypotheses put forward). The tests were placed into priority order and an alpha risk inflation control method was used to avoid overestimating the effect.
The non-inferiority limit of the decrease in HbA1c level (0.4%) is the one habitually used in this type of study.

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[2] Marre M, Shaw J, Brändle M, Bebakar WMW, Kamaruddin NA, Strand J, Zdravkovic M, Le Thi TD, Colagiuri S. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). Diabetic Medicine 2009;26: 268–278.

[3] Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, Zdravkovic M, Düring M, Matthews DR. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes. Diabetes Care 2009;32:84-90.

[4] ZINMAN B, J. GERICH,. BUSE JB, LEWIN A, SCHWARTZ S, RASKIN P, HALE PM, ZDRAVKOVIC M, BLONDE L. Efficacy and safety of the human GLP-1 analog liraglutide in combination with metformin and TZD in patients with type 2 diabetes mellitus (LEAD-4 Met+TZD). Diabetes Care ; published ahead of print March 16, 2009, doi:10.2337/dc08-2124.

[5] Pending publication

[6] John B Buse, Julio Rosenstock, Giorgio Sesti, Wolfgang E Schmidt, Eduard Montanya, Jason H Brett, Marcin Zychma, Lawrence Blonde. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 2009; 374: 39–47.

3.1. Efficacy results

3.1.1. Dual therapy studies: LEAD 1 and LEAD 2

3.1.1.1. LEAD 1 study

Objective and methods:
The primary endpoint of this randomised, double-blind placebo- and active comparator-controlled phase III study, with five parallel groups, was to assess the efficacy and safety of 3 doses of liraglutide (0.6 mg/day, 1.2 mg/day and 1.8 mg/day) combined with glimepiride compared to a placebo and rosiglitazone, after 26 weeks of treatment, in patients with inadequately controlled type 2 diabetes (HbA1c level ≥7% and ≤10%). Among exclusion criteria figured patients with heart disease7, renal impairment8 or hepatic disorders9.

NB: the relevance of the evaluation of the 0.6 mg dose of liraglutide for 26 weeks is debatable as the SPC recommends an initial dose of 0.6 mg that should be increased after 1 week of treatment to 1.2 mg. This also applies to the next study, LEAD 2.

Dosing regimen:
One thousand and forty one patients were randomised to receive, over 26 weeks:
- glimepiride (2 to 4 mg/day) + liraglutide 0.6 mg/day (n=223) or
- glimepiride (2 to 4 mg/day) + liraglutide 1.2 mg/day (n=228) or
- glimepiride (2 to 4 mg/day) + liraglutide 1.8 mg/day (n=234) or
- glimepiride (2 to 4 mg/day) + placebo (n=114) or
- glimepiride (2 to 4 mg/day) + rosiglitazone (4 mg/day (n=232).

Primary endpoint: mean change from baseline in HbA1c after 26 weeks of treatment.

The hypotheses put forward in the protocol were as follows:
- if the superiority of the glimepiride + liraglutide combination over the glimepiride + placebo combination was demonstrated, the non-inferiority of the glimepiride + liraglutide combination compared to the glimepiride + rosiglitazone combination was tested
- if non-inferiority was demonstrated, the superiority of the glimepiride + liraglutide combination over the glimepiride + rosiglitazone combination was tested.

The glimepiride + liraglutide combination could be considered as non-inferior to the glimepiride + rosiglitazone combination if the upper 95% confidence interval limit of the difference in the criterion for the HbA1c level change between the two treatments was less than 0.4%.

NB: the choice of the glimepiride + rosiglitazone dual therapy is questionable. Indeed, in its oral dual therapy indication, in combination with metformin or a sulphonylurea, the efficacy/safety ratio of rosiglitazone has been classified by the Committee as low, in the absence of a proven benefit in terms of morbidity and mortality and a relatively poor safety profile confirmed by recent data in particular in terms of cardiovascular safety and the fracture risk in women. In light of the data available, particularly on safety, the actual clinical benefit has been classified as moderate (see TC opinion of October 15, 2008). This also applies to the LEAD 4 study.

Main secondary endpoints: after 26 weeks of treatment, fasting blood glucose, weight changes and the percentage of patients with HbA1c ≤6.5%

[7] All cardiovascular diseases including a history of myocardial infarction during the 6 months prior to the study and/or heart failure
[8] serum creatinine > 125 µmol/L for men, > 110 µmol/L for women
[9] ALT > 2.5 ULN

Results:

Baseline patient characteristics were similar in each group.
Patients' mean age was 56.1 and most of them suffered from excess weight (mean BMI of 29.9 kg/m²) with an average weight of 81.6 kg. The time since onset of diabetes was on average 7.9 years.
The HbA1c level was 8.4%.

Primary endpoint:

Table 1: changes in HbA1c level after 26 weeks (ITT population):

	glimepiride + liraglutide 0.6 mg	**glimepiride + liraglutide 1.2 mg**	**glimepiride + liraglutide 1.8 mg**	**glimepiride + placebo**	**glimepiride + rosiglitazone**
N	224	223	226	107	224
Mean baseline value of HbA1c (SD)	8.4 (0.98)	8.5 (1.07)	8.5 (0.94)	8.4 (0.96)	8.4 (0.97)
HbA1c at end of treatment	7.9 (1.26)	7.5 (1.20)	7.5 (1.34)	8.7 (1.31)	8.0 (1.33)
Adjusted mean change in HbA1c (SD)	-0.6 (0.07)	-1.08 (0.07)	-1.13 (0.07)	0.23 (0.10)	-0.44 (0.07)
ANCOVA analysis	**Mean difference / comparator**	**95%CI**	**Hypothesis**	**p**	
liraglutide 1.8 mg - placebo	-1.36	[-1.60; -1.13]	Superiority	< 0.0001	
liraglutide 1.8 mg - rosiglitazone (PP population)	-0.61	[-0.81; -0.42]	Non-inferiority		
liraglutide 1.8 mg - rosiglitazone	-0.69	[-0.88; -0.51]	Superiority	< 0.0001	
liraglutide 1.2 mg - placebo	-1.31	[-1.54; -1.08]	Superiority	< 0.0001	
liraglutide 1.2 mg - rosiglitazone (PP population)	-0.57	[-0.76; -0.37]	Non-inferiority		
liraglutide 1.2 mg – rosiglitazone	-0.64	[-0.82; -0.45]	Superiority	< 0.0001	
liraglutide 0.6 mg - placebo	-0.83	[-1.07; -0.60]	Superiority	< 0.0001	
liraglutide 0.6 mg - rosiglitazone (PP population)	-0.12	[-0.31; -0.08]	Non-inferiority		
liraglutide 0.6 mg - rosiglitazone	-0.16	[0.12; 0.46]	Superiority	0.0429	

After 26 weeks of treatment, the decrease in HbA1c levels was greater in glimepiride + liraglutide patients than in glimepiride + placebo patients (difference between liraglutide 1.2 mg/day and 1.8 mg/day and placebo -1.3%, p<0.0001, between liraglutide 0.6 mg/day and placebo 0.8%, p<0.0001).

In accordance with the protocol, the non-inferiority of the glimepiride + liraglutide combination was tested compared to the glimepiride + rosiglitazone combination.
In the liraglutide 0.6mg/day, 1.2 mg/day and 1.8 mg/day treatment groups, the upper limit of the 95% confidence interval was lower than the threshold set. In these treatment groups, the non-inferiority of the glimepiride + liraglutide combination compared to the glimepiride + rosiglitazone combination was established.
These results were confirmed in the ITT population for the liraglutide 1.2 mg/day and 1.8 mg/day treatment groups but not for the liraglutide 0.6 mg/day treatment group.

After 26 weeks of treatment, the decrease in HbA1c levels was greater in glimepiride + liraglutide patients than in glimepiride + rosiglitazone patients (difference between liraglutide 1.2 mg/day and 1.8 mg/day and rosiglitazone: -0.7%, p<0.0001)

The decrease in HbA1c level was maintained until the 12th week of treatment.

Secondary endpoints:

The mean change in fasting blood glucose was -0.72 mmol/l in the liraglutide 0.6 mg + glimepiride group, -1.57 mmol/l in the liraglutide 1.2 mg + glimepiride group, -1.59 mmol/l in the liraglutide 1.8mg + glimepiride group, +1.01 mmol/l in the glimepiride + placebo group and -0.88 mmol/l in the group treated with rosiglitazone +glimepiride.
A statistically significant difference was observed between the three liraglutide + glimepiride treatment groups and the glimepiride + placebo group and between the liraglutide 1.2 mg and 1.8 mg + glimepiride groups and the rosiglitazone + glimepiride group.

Weight decreased by -0.23 kg in the liraglutide 1.8 mg/day group and by -0.10 kg in the placebo group. Weight increased by 0.32 kg in the liraglutide 1.2 mg/day group and by 0.72 kg in the liraglutide 0.6mg group and by 2.11 kg in the rosiglitazone group.
Statistically significant differences were observed between the group treated with liraglutide 0.6 mg/day group and the placebo group and between the three glimepiride + liraglutide groups and the glimepiride + rosiglitazone group.

At the dual therapy stage, the aim is to reduce HbA1c values to < 6.5%.
This goal was achieved by 12.0% of patients treated with 0.6 mg/day liraglutide (28/233), by 21.1% of patients treated with 1.2 mg/day liraglutide (48/228), by 20.5% of patients in the liraglutide 1.8 mg/day group (48/234), by 3.5% of patients in the placebo group (4/114) and by 9.5% of patients in the rosiglitazone group (22/231).

3.1.1.2. LEAD 2 study

Objective and methods:
The primary endpoint of this randomised, double-blind placebo-controlled phase III study with an active comparator, with five parallel groups, was to assess the efficacy and safety of 3 doses of liraglutide (0.6 mg/day, 1.2 mg/day and 1.8 mg/day) combined with metformin compared to a placebo and glimepiride, after 26 weeks of treatment, in patients with inadequately controlled type 2 diabetes (HbA1c levels ≥7% and ≤10%). Among exclusion criteria figured patients with heart disease[10], renal impairment[11] or hepatic disorders[12].

Dosing regimen:
One thousand and ninety one patients were randomised to receive, over 26 weeks:
- metformin (1,500 to 2,000 mg/day) + liraglutide 0.6 mg/day (n=242) or
- metformin (1,500 to 2,000 mg/day) + liraglutide 1.2 mg/day (n=241) or
- metformin (1,500 to 2,000 mg/day) + liraglutide 1.8 mg/day (n=242) or

[10] All cardiovascular diseases including a history of myocardial infarction during the 6 months prior to the study and/or heart failure
[11] serum creatinine > 135 µmol/L for men, > 110 µmol/L for women
[12] ALT > 2.5 ULN

- metformin (1,500 to 2,000 mg/day) + placebo (n=122) or
- metformin (1,500 to 2,000 mg/day) + glimepiride (4 mg/day (n=244).

Primary endpoint: mean change from baseline in HbA1c after 26 weeks of treatment.

The hypotheses put forward in the protocol were as follows:
- if the superiority of the metformin + liraglutide combination over the metformin + placebo combination was demonstrated, the non-inferiority of the metformin + liraglutide combination compared to the metformin + glimepiride combination was tested.
- if non-inferiority was demonstrated, the superiority of the metformin + liraglutide combination over the metformin + glimepiride combination was tested.

The metformin + liraglutide combination was to be considered as non-inferior to the metformin + glimepiride combination if the upper 95% confidence interval limit of the difference in the criterion for the HbA1c level change between the two treatments was less than 0.4%.

Main secondary endpoints: after 26 weeks of treatment, fasting blood glucose, weight change and the percentage of patients with HbA1c ≤6.5%

Results:

Baseline patient characteristics were similar in both groups.
Patients' mean age was 56.8 and most of them were obese (mean BMI of 31.0 kg/m²) with an average weight of 88.6 kg. The time since onset of diabetes was on average 7.4 years.
The HbA1c level was 8.4%.

Primary endpoint:

Table 2: changes in HbA1c level after 26 weeks (ITT population):

	metformin + liraglutide 0.6 mg	**metformin + liraglutide 1.2 mg**	**metformin + liraglutide 1.8 mg**	**metformin + placebo**	**metformin + glimepiride**
N	239	232	236	120	234
Mean baseline value of HbA1c (SD)	8.4 (0.94)	8.3 (1.01)	8.4 (0.97)	8.4 (1.06)	8.4 (1.02)
HbA1c at end of treatment	7.8 (1.12)	7.5 (1.09)	7.5 (1.24)	8.6 (1.44)	7.5 (1.14)
Adjusted mean change in HbA1c (SD)	- 0.69 (0.07)	- 0.97 (0.07)	- 1.00 (0.07)	0.09 (0.09)	- 0.98 (0.07)
ANCOVA analysis	**Mean difference / comparator**	**95%CI**	**Hypothesis**	**P**	
liraglutide 1.8 mg – placebo	- 1.09	[-1.30; -0.88]	Superiority	< 0.0001	
liraglutide 1.8 mg - glimepiride	-0.61	[-0.81; -0.42]	Non-inferiority		
	- 0.09	[-0.26; -0.09]	Superiority	**NS**	
liraglutide 1.2 mg – placebo	- 1.06	[-1.27; -0.85]	Superiority	< 0.0001	
liraglutide 1.2 mg	0.01	[-0.16; 0.19]	Non-inferiority		

– glimepiride	0.01	[- 0.16; 0.18]	Superiority	NA
liraglutide 0.6 mg – placebo	- 0.78	[-0.99; -0.57]	Superiority	< 0.0001
liraglutide 0.6 mg – glimepiride	0.19	[0.01; 0.36]	Non-inferiority	
	-0.29	[0.12; 0.46]	Superiority	NA

After 26 weeks of treatment, the decrease in HbA1c levels was greater in metformin + liraglutide patients than in metformin + placebo patients (difference between liraglutide 1.2 mg/day and 1.8 mg/day and placebo -1.1%, p<0.0001, between liraglutide 0.6 mg/day and placebo -0.8%, p<0.0001).

In accordance with the protocol, the non-inferiority of the metformin + liraglutide combination was tested compared to the metformin + glimepiride combination.
In the liraglutide 0.6mg/day and 1.2 mg/day treatment groups, the upper limit of the 95% confidence interval was lower than the threshold set. In these treatment groups, the non-inferiority of the metformin + liraglutide combination compared to the metformin + glimepiride combination was established.

After 26 weeks of treatment, the superiority of the metformin + liraglutide combination over the metformin + glimepiride combination was not established.

The decrease in HbA1c level was maintained until the 18th week of treatment in the groups treated with liraglutide 1.2 mg and 1.8 mg and in the glimepiride group. In the placebo group, the HbA1c increased up to the 12th week then fell to a level similar to baseline after 26 weeks of treatment.

Secondary endpoints:
The mean change in fasting blood glucose was -1.13 mmol/l in the liraglutide 0.6 mg + metformin group, -1.63 mmol/l in the liraglutide 1.2 mg + metformin group, -1.68 mmol/l in the liraglutide 1.8mg + metformin group, +0.40 mmol/l in the metformin only group and -1.31 mmol/l in the group treated with metformin + glimepiride.
A statistically significant difference was observed between the three liraglutide + metformin groups and the metformin + placebo group. No difference was observed between the liraglutide + glimepiride treatment groups and the metformin + glimepiride group.

Weight decreased by -2.79 kg in the liraglutide 1.8 mg/day group, by -2.58 kg in the liraglutide 1.2mg group, by -1.78 kg in the liraglutide 0.6 mg group and by -1.51 kg in the glimepiride group. It increased by 0.95 kg in the placebo group.
Statistically significant differences were observed between the liraglutide 1.2 mg and 1.8 mg/day treatment groups and the placebo group and between the three metformin + liraglutide groups and the metformin + glimepiride group.

At the dual therapy stage, the aim is to reduce HbA1c values to < 6.5%.
This goal was achieved by 11.2% of patients treated with 0.6 mg/day liraglutide (27/242), by 20.0% of patients treated with 1.2 mg/day liraglutide (48/240), by 24.0% of patients in the liraglutide 1.8 mg/day group (58/242), by 4.1% of patients in the placebo group (5/121) and by 21.9% of patients in the glimepiride group (53/242).

3.1.2. Triple therapy studies: LEAD 4 and LEAD 5

3.1.2.1. LEAD 4 study

Objective and methods:
The primary endpoint of this randomised, double-blind phase III study was to assess the efficacy and safety of 2 doses of liraglutide (1.2 mg/day and 1.8 mg/day) combined with metformin and rosiglitazone, compared to a placebo, after 26 weeks of treatment, in patients with type 2 diabetes inadequately controlled (HbA1c levels ≥7% and ≤10%) by dual metformin and rosiglitazone therapy. Among exclusion criteria figured patients with heart disease13, renal impairment[14] or hepatic disorders[15].

Dosing regimen:
Five hundred and thirty three patients were randomised to receive, over 26 weeks:
- metformin (2,000 mg/day) + rosiglitazone (8 mg/day) + liraglutide 1.2 mg/day (n=178) or
- metformin (2,000 mg/day) + rosiglitazone (8 mg/day) + liraglutide 1.8 mg/day (n=178) or
- metformin (2,000 mg/day) + rosiglitazone (8 mg/day) + placebo (n=177).

Primary endpoint: mean change from baseline in HbA1c after 26 weeks of treatment.

The hypothesis put forward in the protocol was as follows:
- if the superiority of the metformin +rosiglitazone + liraglutide 1.8 mg combination over the metformin + rosiglitazone + placebo combination was demonstrated, the superiority of the metformin + rosiglitazone + liraglutide 1.2 mg combination over the metformin + rosiglitazone + placebo combination was tested.

Main secondary endpoints: after 26 weeks of treatment, fasting blood glucose, weight changes and the percentage of patients with HbA1c ≤7%

Results:

Baseline patient characteristics were similar in each group.
Patients' mean age was 55 and most were obese (mean BMI of 33.5 kg/m²) with an average weight of 96.3 kg. Note that in the placebo group, the weight was higher (98.3 kg on average).
The time since onset of diabetes was on average 9 years.
The HbA1c level was 8.5%.

Primary endpoint:

Table 3: changes in HbA1c level after 26 weeks (ITT population):
OAD = oral antidiabetic

Treatment group	OAD + liraglutide 1.2 mg	OAD + liraglutide 1.8 mg	OAD + placebo
N	174	177	167
Mean baseline value of HbA1c (SD)	8.48 (1.23)	8.56 (1.22)	8.42 (1.17)
HbA1c at end of treatment	7.02 (1.06)	7.08 (1.07)	7.90 (1.29)
Adjusted mean change in HbA1c (SD)	-1.48 (0.08)	-1.48 (0.08)	-0.54 (0.08)

[13] All cardiovascular diseases including a history of myocardial infarction during the 6 months prior to the study and/or heart failure
[14] serum creatinine > 135 µmol/L for men, > 110 µmol/L for women
[15] ALT > 2.5 ULN

ANCOVA analysis	Mean difference / comparator	95%CI	p
Liraglutide 1.2 mg - placebo	-0.941	[-1.123; -0.759]	< 0.0001
Liraglutide 1.8 mg - placebo	-0.936	[-1.119; -0.754]	< 0.0001

After 26 weeks of treatment, the decrease in the HbA1c level was greater in OAD + liraglutide patients than in OAD + placebo patients (difference between liraglutide 1.2 mg/day or 1.8 mg/day and placebo: -0.94%, p<0.0001).

Secondary endpoints:

Fasting blood glucose decreased from 10.07 to 7.71 mmol/l in the liraglutide 1.2 mg + OAD group (n=175), from 10.27 to 7.63 mmol/l in the liraglutide 1.8 mg + OAD group (174) and from 9.95 to 9.50 mmol/l in the placebo + OAD group (n=164).
The differences between the liraglutide groups and placebo group were statistically significant.

Weight decreased by -1.02 kg in the liraglutide 1.2 mg/day group and by -2.02 kg in the liraglutide 1.8 mg/day group. It increased by 0.60 kg in the placebo group.
The difference between the liraglutide 1.2 mg and placebo groups was -1.62 (95%CI [-2.39; -0.85] p<0.0001), and -2.62 (95%CI [-3.39; -1.84], p<0.0001) between the liraglutide 1.8 mg and placebo groups.

At the triple therapy stage, the aim is to reduce HbA1c values to < 7%.
This goal was achieved by 57.5% of patients treated with 1.2 mg/day liraglutide (100/174), by 53.7% of patients in the 1.8 mg/day liraglutide group (95/177), and by 28.1% of patients in the placebo group (47/167).

3.1.2.2. LEAD 5 study

Objective and methods:
The primary endpoint of this randomised, double-blind placebo-controlled and open-label phase III study versus insulin glargine, with three parallel groups, was to assess the efficacy and safety of liraglutide combined with metformin and glimepiride compared to a placebo and insulin glargine, after 26 weeks of treatment, in patients with type 2 diabetes inadequately controlled (HbA1c level ≥7% and ≤10%) by a dual metformin and glimepiride therapy[16]. Among exclusion criteria figured patients with heart disease[17], renal impairment[18] or hepatic disorders[19].

Dosing regimen:
Five hundred and eighty one patients were randomised to receive, over 26 weeks:
- metformin (2,000 mg/day) + glimepiride (2 to 4 mg/day + liraglutide 1.8 mg/day (n=232) or
- metformin (2,000 mg/day) + glimepiride (2 to 4 mg/day) + placebo (n=115) or
- metformin (2,000 mg/day) + glimepiride (2 to 4 mg/day) + insulin glargine 24 IU/day (n=234).

Primary endpoint: mean change from baseline in HbA1c after 26 weeks of treatment.

[16] treated with metformin and glimepiride for at least the past 3 weeks
[17] All cardiovascular diseases including a history of myocardial infarction during the 6 months prior to the study and/or heart failure
[18] serum creatinine > 125 µmol/L for men, > 115 µmol/L for women
[19] ALT > 2.5 ULN

The hypotheses put forward in the protocol were as follows:
- if the superiority of the metformin + glimepiride + liraglutide combination over the metformin + glimepiride + placebo combination was demonstrated, the non-inferiority of the metformin + glimepiride + liraglutide combination compared to the metformin + glimepiride + insulin glargine combination was tested.
- if non-inferiority was demonstrated, the superiority of the metformin + glimepiride + liraglutide combination over the metformin + glimepiride + insulin glargine combination was tested.

The metformin + glimepiride + liraglutide combination was to be considered as non-inferior to the metformin + glimepiride + insulin glargine combination if the upper 95% confidence interval limit of the difference in the criterion for the HbA1c level change between the two treatments was less than 0.4%.

Main secondary endpoints: after 26 weeks of treatment, fasting blood glucose, weight changes and the percentage of patients with HbA1c ≤7%;

Results:

Baseline patient characteristics were similar in each group.
Patients' mean age was 57.5 and most were obese (mean BMI of 30.5 kg/m²) with an average weight of 85.4 kg. The time since onset of diabetes was on average 9.4 years. Around 25% of patients were aged over 65 in all three treatment groups.
The level of HbA1c was 8.2%.

Primary endpoint:

Table 4: changes in HbA1c level after 26 weeks (ITT population):

Treatment group	**OAD + liraglutide**	**OAD + placebo**	**OAD + Insulin glargine**	
n	224	110	225	
Mean baseline value of HbA1c (SD)	8.3 (0.94)	8.3 (0.85)	8.1 (0.93)	
HbA1c at end of treatment	7.0 (1.00)	8.1 (1.31)	7.2 (0.93)	
Adjusted mean change in HbA1c (SD)	- 1.33 (0.09)	- 0.24 (0.11)	- 1.09 (0.09)	
ANCOVA analysis	**Mean difference / comparator**	**95%CI**	**Hypothesis**	**p**
liraglutide - placebo	- 1.09	[-1.28; -0.90]	Superiority	< 0.0001
Liraglutide – insulin glargine (PP population)	- 0.25	[-0.40; -0.09]	Non-inferiority	
Liraglutide - insulin glargine	- 0.24	[-0.39; -0.08]	Superiority	< 0.0001

After 26 weeks of treatment, the decrease in the HbA1c level was greater in OAD + liraglutide patients than in OAD + placebo patients (difference between liraglutide 1.8 mg/day and placebo: -1.09%, 95%CI [-1.28; -0.90]; p<0.0001).

In accordance with the protocol, the non-inferiority of the OAD + liraglutide combination was tested compared to the OAD + insulin glargine combination.
In the PP population, the baseline HbA1c level was 8.3% in the liraglutide group and 8.2% in the placebo and insulin groups. This level decreased by -1.35 in the liraglutide group and by -1.10 in the insulin group, i.e. a difference of -0.25 95%CI [-0.40; -0.09].

The upper limit of the 95% confidence interval was lower than the threshold set. The non-inferiority of the OAD + liraglutide combination compared to the OAD + insulin glargine combination was established.
These results were confirmed in the ITT population.

After 26 weeks of treatment, the decrease in the HbA1c level was greater in OAD + liraglutide patients than in OAD + insulin patients (difference between liraglutide 1.8 mg/day and insulin: -0.24%, 95%CI [-0.39; -0.08]; p<0.0001).

Secondary endpoints:

Fasting blood glucose decreased from 9.1 to 7.7 mmol/l in the liraglutide + OAD group (n=225), increased from 9.4 to 10.0 mmol/l in the placebo + OAD group (n=111) and decreased from 9.1 to 7.4 mmol/l in the insulin glargine +OAD group (n=226), i.e. a difference between liraglutide and placebo of -2.1 mmol/l (95%CI [-2.5; -1.6] p<0.0001). The difference between liraglutide and insulin was not statistically significant.

Weight decreased by -1.81 kg in the liraglutide group and by -0.42 kg in the placebo group. It increased by +1.62 kg in the insulin glargine group[20].
The difference between the liraglutide and placebo groups was -1.39 (95%CI [-2.10; -0.69] p=0.0001, and -3.43 (95%CI [-4.00; -2.86], p<0.0001) between the liraglutide and insulin groups.

At the triple therapy stage, the aim is to reduce HbA1c values to < 7%.
This goal was achieved by 53.1% of patients in the liraglutide group (119/224), by 15.3% of patients in the placebo group (17/111), and by 45.8% of patients in the insulin group (103/226).

3.1.3. Study versus exenatide: LEAD 6 study

Objective and methods:
Randomised, open-label, phase III study, whose primary endpoint of which was to establish the non-inferiority of liraglutide combined with metformin and/or a sulphonylurea compared to exenatide, after 26 weeks of treatment, in patients with type 2 diabetes inadequately controlled (HbA1c level ≥7% and ≤11%) by metformin and/or a sulphonylurea for the past 3 months at least. Among exclusion criteria figured patients with heart disease21, renal impairment22 or hepatic disorders[23].
This study involved an open-label extension phase lasting 14 weeks to assess the effect of switching from exenatide to liraglutide.

Dosing regimen:
Four hundred and sixty four patients were randomised to receive, over 26 weeks:
- metformin ± sulphonylurea + liraglutide 1.8 mg/day in 1 injection (n=233) or
- metformin ± sulphonylurea + exenatide 20 µg/day in 2 injections (n=231).

NB: information concerning the dosage of metformin and the sulphonylurea administered is not supported. The protocol specifies that the patients included must be inadequately controlled by metformin and/or a sulphonylurea for the past 3 months at least at the maximum tolerated dose. Dual therapy with metformin + sulphonylurea was administered to 63% of patients.

Primary endpoint: mean change from baseline in HbA1c after 26 weeks of treatment.
If the non-inferiority was demonstrated, the protocol foresaw a superiority test.

[20] There is a decrease in mean weight up to the 12th week of treatment in the liraglutide group, up to the 8th week in the placebo group. The increase in weight was observed throughout the study in the insulin group.
[21] All cardiovascular diseases including a history of myocardial infarction during the 6 months prior to the study and/or heart failure
[22] serum creatinine > 135 µmol/L for men, > 115 µmol/L for women
[23] ALT > 2.5 ULN

The metformin + sulphonylurea + liraglutide combination was to be considered as non-inferior to the metformin + sulphonylurea + exenatide combination if the upper 95% confidence interval limit of the difference in the criterion for the HbA1c level change between the two treatments was less than 0.4%.

Main secondary endpoints: after 26 weeks of treatment, fasting blood glucose, weight changes and the percentage of patients with HbA1c ≤6.5% and <7%.

Results:

Baseline patient characteristics were similar in each group.
Patients' mean age was 56.7 and most of them were obese (mean BMI of 32.9 kg/m²) with an average weight of 93.1 kg. The time since onset of diabetes was on average 8.2 years.
The rate of HbA1c was 8.2%.
Around one-third of patients were treated with one OAD (metformin or sulphonylurea) and two-thirds were treated with combined OADs (metformin + sulphonylurea).

Primary endpoint:

Table 5: changes in HbA1c level after 26 weeks (ITT population):

Treatment group	**OAD + liraglutide 1.8 mg**	**OAD + exenatide 20 µg**		
n	227	226		
Mean baseline value of HbA1c (SD)	8.2 (1.00)	8.1 (0.96)		
HbA1c at end of treatment	7.0 (0.91)	7.3 (1.03)		
Adjusted mean change in HbA1c (SD)	- 1.12 (0.08)	- 0.79 (0.08)		
ANCOVA analysis	**Mean difference / comparator**	**95%CI**	**Hypothesis**	**p**
liraglutide + exenatide (PP population)	- 0.29	[- 0.45; - 0.13]	Non-inferiority	
liraglutide - exenatide	- 0.33	[- 0.47; - 0.18]	Superiority	< 0.0001

In the PP population, the baseline HbA1c level was 7.0% in the liraglutide group and 7.2% in the exenatide group. This level decreased by -1.16 in the liraglutide group and by -0.87 ~~kg~~ in the exenatide group, i.e. a difference of -0.29% 95%CI [-0.45; -0.13].
The upper limit of the 95% confidence interval was lower than the threshold set. The non-inferiority of the OAD + liraglutide combination compared to the OAD + exenatide combination was established.
These results were confirmed in the ITT population.

After 26 weeks of treatment, the decrease in the HbA1c level was greater in OAD + liraglutide patients than in OAD + exenatide patients (difference between liraglutide and exenatide: -0.33%, 95%CI [-0.47; -0.18]; p<0.0001).

In both treatment groups, the HbA1c level decreased significantly up to the 12th week, more in the liraglutide 1.8 mg group than in the exenatide 20 µg group. From the 12th week of treatment this level rose in the two treatment groups.

Secondary endpoints:

Fasting blood glucose decreased from 9.78 to 7.91 mmol/l in the liraglutide group and from 9.47 to 8.80 mmol/l in the exenatide group, i.e. a difference between liraglutide and exenatide of -1.01 mmol/l (95%CI [-1.37; -0.65] p <0.0001).

Weight decreased by -3.24 kg in the liraglutide group and by -2.87 kg in the exenatide group. No significant difference was observed between the two treatment groups.

The percentage of patients with an HbA1c level of ≤6.5% (dual therapy endpoint) was 35% in the liraglutide group and 21% in the exenatide group (p<0.05).
At the triple therapy stage, the aim is to reduce HbA1c values to <7%.
After 26 weeks of treatment, the percentage of patients reaching an HbA1c level of <7% was significantly greater in the liraglutide 1.8 mg group than in the exenatide group (54.2% compared to 43.4%; p=0.0015).

Results of 14-week extension phase[24]
Primary endpoint:
After 40 weeks of treatment, the decrease in the HbA1c level compared to baseline was -1.29 (95%CI [1.43; -1.16]; p<0.0001) in the group treated with liraglutide for 40 weeks, and -1.17 (95%CI [-1.31; -1.03]: p<0.0001) in the group previously treated with exenatide (treated with liraglutide for the past 14 weeks).
The difference compared to the 26th week of treatment was not significant in the group treated with liraglutide for the past 40 weeks. There was a difference of -0.32 (95%CI [-0.41; -0.24]; p<0.0001) in the group treated with liraglutide for the past 14 weeks.

Other primary efficacy endpoints:
After 40 weeks' treatment, the decrease in fasting blood glucose compared to baseline in the group treated with liraglutide for 40 weeks was -2.2 (95%CI [-2.52; -1.87]; p<0.0001) and -1.7 (95%CI [-2.02; -1.29]: p<0.0001) in the group treated with liraglutide for the past 14 weeks.
The difference compared to the 26th week of treatment was not significant in the group treated with liraglutide for the past 40 weeks. There was a difference of -0.9 (95%CI [-1.27; -0.63]; p<0.0001) in the group treated with liraglutide for the past 14 weeks.

Between the 40th week of treatment and baseline, weight decreased by -3.2 kg (95%CI [-3.84; -2.64]; p<0.0001) in the group treated with liraglutide for 40 weeks and by -3.4 kg (95%CI [-3.89; -2.83]: p<0.0001) in the group treated for the past 14 weeks.
Between the 40th and 26th week of treatment, weight decreased by -0.4 kg (95%CI [-0.67; -0.10]; p=0.0089) in the group treated with liraglutide for 40 weeks and -0.9 kg (95%CI [-1.18; -0.60]; p<0.0001) in the group treated for the past 14 weeks.

[24] 386 patients took part in this extension phase: 200 from the liraglutide group and 186 from the exenatide group

3.2. Safety data

3.2.1. From SPC

In five large long-term clinical trials over 2500 patients have received treatment with Victoza alone or in combination with metformin, a sulphonylurea (with or without metformin) or metformin plus rosiglitazone.

The most frequently reported adverse reactions during clinical trials were gastrointestinal disorders: nausea and diarrhoea were very common, whereas vomiting, constipation, abdominal pain, and dyspepsia were common. At the beginning of Victoza therapy, these gastrointestinal adverse reactions may occur more frequently. These reactions usually diminish within a few days or weeks on continued treatment. Headache and nasopharyngitis were also common. Furthermore, hypoglycaemia was common, and very common when Victoza is used in combination with a sulphonylurea. Major hypoglycaemia has primarily been observed when combined with a sulphonylurea.

Most episodes of confirmed hypoglycaemia in clinical studies were minor. No episodes of major hypoglycaemia were observed in the study with Victoza used as monotherapy. Major hypoglycaemia may occur uncommonly and has primarily been observed when Victoza is combined with a sulphonylurea (0.02 events/subject year). Very few episodes (0.001 events/subject year) were observed with administration of Victoza in combination with oral antidiabetics other than sulphonylureas.

Gastrointestinal adverse reactions:
When combining Victoza with metformin, 20.7% of patients reported at least one episode of nausea, and 12.6% of patients reported at least one episode of diarrhoea. When combining Victoza with a sulphonylurea, 9.1% of patients reported at least one episode of nausea and 7.9% of patients reported at least one episode of diarrhoea. Most episodes were mild to moderate and occurred in a dosedependent fashion. With continued therapy, the frequency and severity decreased in most patients who initially experienced nausea.

Immunogenicity
Consistent with the potentially immunogenic properties of medicinal products containing proteins or peptides, patients may develop anti-liraglutide antibodies following treatment with Victoza. On average, 8.6% of patients developed antibodies. Antibody formation has not been associated with reduced efficacy of Victoza. Few cases (0.05%) of angioedema have been reported during all long-term clinical trials with Victoza.

Injection site reactions
Injection site reaction has been reported in approximately 2% of subjects receiving Victoza in long-term (26 weeks or longer) controlled trials. These reactions have usually been mild and did not lead to discontinuation of Victoza.

Pancreatitis
Few cases (<0.2%) of acute pancreatitis have been reported during long-term clinical trials with Victoza. A causal relationship between Victoza and pancreatitis can neither be established nor excluded.

Thyroid events
The overall rates of thyroid adverse events in all intermediate and long-term trials are 33.5, 30.0 and 21.7 events per 1000 subject years of exposure for total liraglutide, placebo and total comparators; 5.4, 2.1 and 0.8 events, respectively concern serious thyroid adverse events.
In liraglutide-treated patients, thyroid neoplasms, increased blood calcitonin and goiters are the most frequently thyroid adverse events and were reported in 0.5%, 1% and 0.8% of patients respectively.

3.2.2. LEAD 6 study versus exenatide

Adverse effects were reported in 74.9% of patients in the liraglutide group and 78.8% of patients in the exenatide group.
The main adverse effects observed were gastrointestinal (mainly diarrhoea and nausea) in roughly 45% of patients in each group and infections (essentially nasopharyngitis) in 35% of patients in each group.
25.5% of liraglutide patients and 33.6% of exenatide patients experienced at least one episode of hypoglycaemia.

Treatment was discontinued due to adverse effects in 9.8% of patients in the liraglutide group and 13.4% of patients in the exenatide group.

Around 58% of patients had exenatide antibodies at the end of the study (109/187 patients) and 3/202 patients had liraglutide antibodies. In 5 exenatide patients and in 2 liraglutide patients, these antibodies cross reacted with native GLP-1. A positive neutralising effect was observed in 12 patients in the exenatide group.

In the extension phase, around 37% of patients in each treatment group suffered adverse events, mainly nausea and diarrhoea, which affected around 15% of patients. Thirteen liraglutide patients and 22 exenatide patients experienced at least one hypoglycaemic episode.

3.3. Conclusion

To support its request, the company submitted five clinical studies: two studies assessing the efficacy of liraglutide in dual therapy, two in triple therapy, compared to placebo and an active comparator, and one study compared to exenatide in dual and triple therapy, the other ~~a~~ GLP-1 analogue available.

In dual therapy, the primary endpoint of randomised, double-blind placebo-controlled phase III studies with an active comparator was to assess after 26 weeks of treatment the efficacy and safety of 3 doses of liraglutide (0.6 mg/day, 1.2 mg/day and 1.8 mg/day) combined with glimepiride compared to a placebo and compared to rosiglitazone (LEAD 1 study, n=1,401) or combined with metformin compared to a placebo and compared to glimepiride (LEAD 2 study, n=1,091).
In these studies, the mean age of patients was relatively low (between 55 and 57) and the BMI higher (between 30 and 33 kg/m^2) compared to the values observed in the French population of type 2 diabetic patients (mean age 65, mean BMI 29 kg/m^2), according to the ENTRED[25] 2007-2010 study data.
The dosages of the antidiabetic drugs combined with liraglutide are in line with those recommended in their SPCs. However, the dosages of rosiglitazone in the LEAD 1 study, of glimepiride in LEAD 1 and LEAD 5, and of insulin in LEAD 5 are low. The doses of sulphonylurea and insulin could have been higher, which would most likely have increased their efficacy, but also increased hypoglycaemia.

After 26 weeks' treatment, the decrease in HbA1c levels (primary endpoint) was:

- -1.3% (p<0.0001) in patients taking glimepiride + liraglutide (1.2 mg/day and 1.8 mg/day) compared to those taking glimepiride + placebo in LEAD 1
- -0.7% (p<0.0001) in patients taking glimepiride + liraglutide (1.2 mg/day and 1.8 mg/day) compared to those taking glimepiride + rosiglitazone in LEAD 1
- -1.1% (p<0.0001) in patients taking metformin + liraglutide (1.2 mg/day and 1.8 mg/day) compared to those taking metformin + placebo in LEAD 2.

After 26 weeks of treatment, the superiority of the metformin + liraglutide combination compared to the metformin + glimepiride combination was not established.

[25] National Representative Control Sample of people with diabetes in France. 2007-2010

In triple therapy in the randomised, double-blind LEAD 4 study, the primary endpoint was to assess the efficacy and safety of 2 doses of liraglutide (1.2 mg/day and 1.8 mg/day) combined with metformin and rosiglitazone, compared to a placebo, in 533 patients with type 2 diabetes.
After 26 weeks of treatment, the decrease in the HbA1c level was greater in metformin + rosiglitazone + liraglutide patients than in metformin + rosiglitazone + placebo patients (difference between liraglutide 1.2 mg/day or 1.8 mg/day and placebo: -0.94%, p<0.0001).
In triple therapy, in the randomised, double-blind placebo-controlled and open-label LEAD 5 study compared to insulin glargine, the primary endpoint was to assess the efficacy and safety of liraglutide combined with metformin and glimepiride compared to a placebo and insulin glargine, in 581 patients with type 2 diabetes inadequately controlled by a dual therapy of metformin and glimepiride.
After 26 weeks of treatment, the decrease in the HbA1c level was greater in metformin + glimepiride + liraglutide patients than in metformin + glimepiride + placebo patients (difference between liraglutide 1.8 mg/day and placebo: -1.09%, 95%CI [-1.28; -0.90]; p<0.0001).
After 26 weeks of treatment, the decrease in the HbA1c level was greater in metformin + glimepiride + liraglutide patients than in metformin + glimepiride + insulin patients (difference between liraglutide 1.8 mg/day and insulin: -0.24%, 95%CI [-0.39; -0.08]; p<0.0001).

In the LEAD 6 study comparing to exenatide, the primary endpoint was to establish the non-inferiority of liraglutide combined with metformin and/or a sulphonylurea compared to exenatide, after 26 weeks of treatment, in 464 patients with type 2 diabetes. If non-inferiority was established, a superiority test was conducted.
The non-inferiority of the metformin ± sulphonylurea + liraglutide combination compared to the metformin ± sulphonylurea + exenatide combination was established.
After 26 weeks of treatment, the decrease in the HbA1c level was greater in patients taking metformin ± sulphonylurea + liraglutide than in those taking metformin ± sulphonylurea + exenatide but the difference between these 2 GLP-1 analogues is small (difference between liraglutide and exenatide: -0.33%, 95%CI [-0.47; -0.18]; p<0.0001).
Overall, the effect of liraglutide in reducing the HbA1c level is roughly the same as that observed with existing recommended alternatives[26].
In the LEAD 1, LEAD 2 and LEAD 4 studies, the results do not show liraglutide as having an additional effect at a dose of 1.8 mg compared to the 1.2 mg dose.

As for safety, the most common adverse events observed were gastrointestinal disorders (mainly nausea and diarrhoea) and infections (nasopharyngitis).
Hypoglycaemia is less frequent with VICTOZA except when combined with a sulphonylurea.
For the analysis of the weight change criterion, statistically significant differences were observed between the three glimepiride + liraglutide treatment groups and the glimepiride + rosiglitazone group in the LEAD 1 study, between the groups treated with liraglutide 1.2 mg and 1.8 mg/day and the placebo group in the LEAD 2 and LEAD 4 studies, between the three metformin + liraglutide treatment groups and the metformin + glimepiride group in the LEAD 2 study, and between the liraglutide and placebo and liraglutide and insulin groups in the LEAD 5 study. Weight loss varied between 0.2 and 3.2 kg.
In LEAD 6, weight decreased by -3.24 kg in the liraglutide group and by -2.87 kg in the exenatide group. The difference between the two treatment groups was not significant.
Liraglutide appears to be less immunogenic than exenatide. This is due to the fact that liraglutide is 97% homologous with native GLP-1, compared to 50% for exenatide.

[26] The mean changes in HbA1c levels observed are:
- -1 to -1.5% with metformin
- -1 to -1.5% with sulphonylureas
- -1% with glitazones
- -0.8% with glinides
- -0.7% with gliptins

-0.5 to 1% with alpha-glucosidase inhibitors

The European risk management plan, namely through 6 studies, involves the monitoring of pancreatitis, thyroid cancer, infections, renal impairment and hepatic impairment.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Type 2 diabetes is a chronic disease with potentially serious complications.
VICTOZA is used for the treatment of hyperglycaemia.
The efficacy/adverse effects ratio in dual therapy and triple therapy is high.
The decrease in the HbA1c level is close to the value habitually observed with other antidiabetic drugs. However, there is no long-term safety data, particularly concerning the risk of pancreatitis and adverse thyroid effects.
VICTOZA is an additional means of treatment for the management of type-2 diabetes patients. There are alternative medications.

Public health benefit:
The public health burden of type 2 diabetes is substantial. The public health burden corresponding to the subpopulation of patients likely to benefit from VICTOZA is moderate.
Improving the therapeutic management of type-2 diabetics is a public health need.
In the absence of any demonstration concerning morbidity and mortality and long-term data on the control of HbA1c levels in patients treated with VICTOZA, the impact of VICTOZA is not directly quantifiable.
However, in view of the results of trials on HbA1c reduction associated with weight loss, a low theoretical impact may be expected in the short term in type-2 diabetic patients, particularly obese patients (BMI ≥ 30).
A positive effect is expected in patients inadequately controlled with a single therapy.
In patients inadequately controlled with an oral dual therapy, the absence of dose titration with VICTOZA and the use of a fixed dose mean that a positive impact may be expected in patients whose HbA1c is inadequately controlled by insulin, for which a dosage increase is not optimal due to the risk of hypoglycaemia.
There is also no guarantee that investigational data can be transposed, particularly because:
- the compliance with VICTOZA, a treatment requiring one injection a day and frequently causing gastrointestinal disorders, is not assured;
- thirty French centres were included in four of the six trials submitted, but the exact (probably low) number of French patients included in these centres is not specified. The characteristics of the population studied are appreciably different to the diabetic population in France (the trial population was younger, had been living with diabetes for less time, and their HbA1c level was higher).
VICTOZA is not expected to benefit public health when a single oral therapy fails. It is expected that this product will provide a low public health benefit when oral dual therapy fails.

The actual benefit of VICTOZA in its indication is substantial.

4.2. Improvement in actual benefit

In dual therapy, the superiority of VICTOZA in reducing the HbA1c level was established in combination with a sulphonylurea (glimepiride) over the sulphonylurea + rosiglitazone combination, the clinical relevance of which is debatable.
In triple therapy, in combination with metformin and a sulphonylurea, VICTOZA was superior to insulin glargine at a non-optimal dose.
However, VICTOZA was not superior to the dual therapy of choice, metformin + sulphonylurea.

Combined with metformin and/or a sulphonylurea, the superiority of VICTOZA at a dose of 1.8 mg compared to exenatide at a dose of 20 µg (BYETTA) was established, but the difference between these two GLP-1 analogues is small. One advantage of VICTOZA is the once daily administration, at any time of the day.
The safety profile is positive, particularly in terms of decreased risk of hypoglycaemia and weight loss. However, there is uncertainty over the long-term safety, the risk of pancreatitis and thyroid adverse effects.

In light of all these facts, the Transparency Committee feels that VICTOZA provides a minor improvement in actual benefit (IAB IV) in the management of patients with type 2 diabetes taking dual and triple therapy.

4.3. Therapeutic use

The goals of treatment are:

- to control blood glucose: control HbA1c
- to control associated risk factors.

According to the guideline "Medication for type 2 diabetes" published by Afssaps and HAS in November 2006, the initial treatment of type 2 diabetes is based on an assessment of and realistic changes in lifestyle habits (diet and exercise). Adopting an active lifestyle and nutritional planning are essential measures at all stages of diabetes management.
It may be necessary to use oral antidiabetics when dietary and lifestyle measures (DLM) alone do not control blood glucose levels: HbA1c >6%. There are 4 classes: metformin, intestinal alpha-glucosidase inhibitors (AGI), insulin secretors and glitazone.
These guidelines do not include five antidiabetic treatments whose MAs were granted after 2006: two GLP-1 analogues: exenatide (MA November 2006) and liraglutide (MA June 2009), three DPP-4 inhibitors: sitagliptin (MA March 2007), vildagliptin (MA September 2007) and saxagliptin (MA October 2009).

At the dual oral therapy stage (refractory to single therapies: HbA1C >6.5% after 6 months of one of the single therapies at maximum dose), one of the following dual therapies may be proposed:
- metformin + insulin secretor (sulphonylurea or glinide)
- metformin + glitazone
- metformin + alpha-glucosidase inhibitor
- insulin secretor + glitazone, in the case of known and persistent intolerance to metformin or a contraindication to metformin
- or insulin secretor + alpha-glucosidase inhibitors (if there is major postprandial hyperglycaemia although this combination is less effective on HbA1c than the other combinations).

The choice of combination must take into account the safety and contraindications of each drug class, the patient's age, the risk and degree of hypoglycaemia and the specific clinical and biological profile of each patient (professional consensus).

The different stages of treatment are summarised in the table below.

Therapeutic use (chronic condition 8 - Type 2 diabetes)[27]

HbA1c levels	Treatment	Target HbA1c
HbA1c between 6% and 6.5% despite DLM	Single metformin therapy (or AGI in the case of intolerance or contraindication)	<6.5%
HbA1c >6.5% despite DLM	Single metformin therapy or insulin secretor or AGI	Maintain HbA1c <6.5%
HbA1c >6.5% despite single therapy and DLM	Dual therapy	Reduce HbA1c to <6.5%
HbA1c >7% despite dual therapy and DLM	- Triple therapy: metformin + insulin secretor + glitazone or - insulin + metformin ± other OAD except glitazone	Reduce HbA1c to <7%
HbA1c >8% despite triple therapy and DLM	insulin + metformin ± other OAD except glitazone	Reduce HbA1c to <7%

DLM: Diet and lifestyle measures; OAD: oral antidiabetics; AGI: intestinal alpha-glucosidase inhibitors

Place of Victoza in therapeutic strategy

In dual therapy, VICTOZA is a new therapeutic alternative to other dual therapies recommended. However, the superiority over the dual therapy of choice, metformin + sulphonylurea, has not been established, only the non-inferiority.

In triple therapy, alternative treatments are metformin + sulphonylurea + glitazone combinations, metformin + sulphonylurea + exenatide, combinations of insulin with other oral antidiabetic drugs except glitazone. We have at our disposal one study comparing VICTOZA to insulin glargine and exenatide.

In the absence of direct comparisons to all the triple therapies available, none can be recommended over another.

4.4. Target population

According to the MA indication, the target population of VICTOZA corresponds to patients with type 2 diabetes treated:

- with metformin or a sulphonylurea with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformine or sulphonylurea (HbA1c >6.5%).
- with metformin combined with a sulphonylurea or metformin combined with a thiazolidinedione with insufficient glycaemic control despite dual therapy (HbA1c >7%).

Data from the study conducted using the permanent sample of affiliates of the National Insurance Scheme (EPAS) established by the Health Insurance Fund for Salaried Workers (CNAMTS)[28] indicates that the prevalence of diabetes treated in Metropolitan France for all schemes was 3.8% in 2005 and that the mean annual increase noted between 2000 and 2005 was 5.7%. On the basis of these percentages and assuming that the mean annual increase between 2000 and 2005 was the same between 2005 and 2006 and remained constant in 2006 and 2007, the number of diabetic patients treated in 2007 would have been approximately 2,485,000[29].

91% of these patients are type 2 diabetics (ENTRED 2001-2003 – diabetes network No. 29 – September 2006).

[27] Management of diabetes: type 2 diabetes. Guide for physicians – Chronic condition, HAS - May 2006

[28] Diabète traité, quelles évolutions entre 2000 et 2005, Prat Organ Soins 2007; 38 (1):1-12

[29] On the basis of the INSEE population on January 1, 2008

According to the partially published results of the ECODIA 2 study (diabetes network No. 31 – March 2007), 83.2% of type 2 diabetics are treated with an oral antidiabetic without insulin, 24.6% with metformin alone and 21.6% with a sulphonylurea alone.
The ECODIA 2 study data indicates that 68% of patients have HbA1c levels above 6.5%.
The percentage of patients with a contraindication or intolerance to metformin is not well known. We hypothesise that 20% of patients are concerned.

Dual oral therapy:
- 83.2% of type 2 diabetics are treated with oral antidiabetics without insulin, of which 24% take metformin alone and 21.6% a sulphonylurea alone.
- 68% of patients have an HbA1c level above 6.5%.

The number of patients whose diabetes is inadequately controlled by a diet and physical exercise and by metformin treatment properly taken is therefore thought to be **307,000**.
Based on this, the population of patients refractory to a single sulphonylurea therapy properly taken and for whom metformin is inappropriate due to intolerance or a contraindication is thought to be **55,300**.

Triple therapy:
- 83.2% of type 2 diabetics are treated with oral antidiabetics without insulin, of which 24.6% take dual therapy of metformin and a sulphonylurea and 6.4% dual therapy of metformin and glitazone.
- 51.5% of patients have an HbA1c above 7%.

On this basis, the population of patients refractory to a dual therapy of metformin and a sulphonylurea properly taken is therefore **238,400**, and the number of patients refractory to a dual therapy of metformin and glitazone properly taken is **62,000**.

The Committee repeats that it is not advisable for patients with moderate to severe renal impairment or patients with hepatic impairment to use VICTOZA.
These conditions are contraindications or come under the precautions for use of metformin, sulphonylureas and glitazones but are difficult to quantify.
Therefore, the aforementioned population size is a maximum estimation of the population corresponding to the MA.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of products reimbursed by National Insurance and on the list of products approved for use in hospitals and various public services in the indications and the dosage of the MA.

The Transparency Committee requests that a study be conducted (see appendix) on a representative sample of French type-2 diabetes patients treated with VICTOZA. The aim of this study will be to describe the following aspects under actual treatment conditions:
- the characteristics of the patients treated (including age, BMI and baseline HbA1c level);
- the conditions of use for this product (indication, dosage and dosage adaptations, concomitant treatments, blood glucose monitoring procedures, etc.);
- the treatment compliance rate;
- the frequency of treatment discontinuations and reasons;
- the change in HbA1c and weight, and long-term safety (2 years).

The duration of the study, to be determined by a scientific committee, should be duly justified, and it should be sufficient to answer the Transparency Committee's questions.
If scheduled or ongoing studies, in particular within the scope of the European Risk Management plan, do not answer all the questions raised by the Transparency Committee, a specific study must be conducted.

4.5.1. Packaging: appropriate for the prescription conditions
4.5.2. Reimbursement rate: 65%

APPENDICE

PROOF OF POST-MARKETING STUDY REQUEST

VICTOZA® (liraglutide)

For VICTOZA (liraglutide) in the treatment of T2D, the "Public Health Benefit and Post-marketing Studies" group (ISPEP), during its October work session, evaluated the expected public health benefit (EPHB) for this product and asked that a post-marketing study be conducted.

This request was warranted by a lack of data in the application to the Transparency Committee in the three following areas:

- absence of short, medium and long term morbidity and mortality data;
- absence of medium and long-term data on HbA1c, weight and safety;
- absence of medium and long-term comparative data, particularly in comparison to BYETTA (especially as the criteria used for this short-term comparison were intermediate: changes in HbA1c and weight).

Such data would confirm the hypothesis that under real conditions of use, VICTOZA can provide a long-term benefit in terms of morbidity (and even mortality) compared to the existing treatment strategy. This hypothesis supports the IACB and EPHB of VICTOZA.

Initially, the ISPEP group asked that the impact of VICTOZA on the morbidity of patients treated be evaluated under real conditions of use, through a study comparing VICTOZA to other antidiabetic treatments, based on morbidity criteria (macroangiopathic – cardiovascular – and renal and retinal microangiopathic complications), on a representative sample of French patients with type 2 diabetes not controlled with single or dual therapy and whose diabetes dates back to more than 5 years[30]).

However, there were discussions among the Transparency Committee when the final decision regarding VICTOZA was adopted. It appeared necessary, to be fair, to take into account prior post-marketing study requests for other products.

Hence, the Committee maintains its request for a post-marketing study for VICTOZA but its wording will be identical to that of the other studies concerning products with a similar therapeutic aim already in progress.

[30] This endpoint included patients at an already advanced stage of their condition who had a higher risk of macro and microangiopathic complications, in order to increase the number of events observed.