HAUTE AUTORITÉ DE SANTÉ

**The legally binding text is the original French version**

**TRANSPARENCY COMMITTEE**

OPINION

28 February 2007

**BYETTA 5µg, solution for injection in prefilled pen**
**Pack of 1 pen (CIP Code: 378 092-6)**
**Pack of 3 pens (CIP Code: 378 093-2)**

**BYETTA 10µg, solution for injection in prefilled pen**
**Pack of 1 pen (CIP Code: 378 094-9)**
**Pack of 3 pens (CIP Code: 378 095-5)**

**Applicant: LILLY**

exenatide

ATC code: A10BX04

List 1

Date of Marketing Authorisation: 20 November 2006

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

Medical, Economic and Public Health Assessment Division

# 1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

## 1.1. Active ingredient

exenatide

## 1.2. Originality

Exenatide is the first substance to be marketed in the new drug category of incretin mimics.

## 1.3. Indication

BYETTA is indicated in the 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 treatments.

## 1.4. Dosage

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. Doses higher than 10µg BID are not recommended.

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. If an injection is missed, the treatment should be continued with the next scheduled dose.
Each dose should be administered as a subcutaneous injection in the thigh, abdomen, or upper arm.

BYETTA is recommended for use in patients with type 2 diabetes mellitus who are already receiving metformin and/or a sulphonylurea.
When BYETTA is added to existing metformin therapy, the current dose of metformin can be maintained as no increased risk of hypoglycaemia is anticipated, compared to metformin alone.
When BYETTA is added to sulphonylurea therapy, a reduction in the dose of sulphonylurea should be considered to reduce the risk of hypoglycaemia.
The dose of BYETTA does not need to be adjusted on a day-to-day basis depending on self-monitored glycaemia. However, blood glucose self-monitoring may become necessary to adjust the dose of sulphonylureas.

Limited experience exists concerning the combination of BYETTA with thiazolidinediones.

*Specific patient groups*

*Elderly*
BYETTA should be used with caution and dose escalation from 5 µg to 10 µg should proceed conservatively in patients >70 years of age. The clinical experience in patients >75 years of age is very limited.

*Patients with renal impairment*
No dosage adjustment of BYETTA is necessary in patients with mild renal impairment (creatinine clearance between 50 and 80 ml/min).
In patients with moderate renal impairment (creatinine clearance: 30-50 ml/min), dose escalation from 5 µg to 10 µg should proceed conservatively.

BYETTA is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 ml/min).

*Patients with hepatic impairment*
No dosage adjustment of BYETTA is necessary in patients with hepatic impairment.

*Children and adolescents*
There is no clinical experience in children and adolescents under 18 years of age.

## 2 SIMILAR MEDICINAL PRODUCTS

### 2.1. ATC Classification (2006)

| | |
|---|---|
| A | Digestive tract and metabolism |
| A10 | Drugs used in diabetes |
| A10B | Blood glucose lowering drugs, excl. insulins |
| A10BX | Other blood glucose lowering drugs, excl. insulins |
| A10BX04 | Incretin mimics |

### 2.2. Medicines in the same therapeutic category

None.

### 2.3. Medicines with a similar therapeutic aim

Medicinal products indicated in type-2 diabetic patients who have not achieved adequate glycaemic control at the maximum tolerated doses of oral metformin or sulphonylurea monotherapy:

- hypoglycaemic sulphonylureas
- biguanides
- glitazones
- intestinal alpha-glucosidase inhibitors
- repaglinide (NOVONORM): indicated in combination with metformin in type-2 diabetics not adequately controlled by metformin alone.

Medicinal products indicated in type-2 diabetic patients who have not achieved adequate glycaemic control at the maximum tolerated doses of combined oral metformin and sulphonylurea:

- Glitazones:

  Rosiglitazone (AVANDIA) may be prescribed in oral tritherapy in combination with metformin and a hypoglycaemic sulphonylurea in patients (particularly overweight patients) who are inadequately controlled by oral bitherapy.
  Rosiglitazone exists in the form of a fixed combination with metformin (AVANDAMET).
  Pioglitazone (ACTOS) has obtained a marketing authorisation for tritherapy use, but it is not included on the list of medicinal products qualifying for reimbursement in this indication.
- Insulins.

## 3 ANALYSIS OF AVAILABLE DATA

The applicant has submitted the results of 6 clinical studies:

- three placebo-controlled studies after failure of oral antidiabetics:
  - study 112 on the use of BYETTA in combination with metformin in patients inadequately controlled by metformin alone
  - study 113 on the use of BYETTA in combination with a sulphonylurea in patients inadequately controlled by sulphonylureas
  - study 115 on the use of BYETTA in combination with metformin and a sulphonylurea in patients inadequately controlled by a combination of metformin and a sulphonylurea;
- three comparative studies versus insulin:
  - study GWAA on the use of BYETTA in comparison with insulin glargine (LANTUS) in combination with oral metformin + sulphonylurea bitherapy
  - study GWAD on the use of BYETTA in comparison with biphasic insulin aspart (Novomix 30) in combination with oral metformin + sulphonylurea bitherapy
  - study GWAO on the use of BYETTA in comparison with insulin glargine (LANTUS) in combination with oral metformin or sulphonylurea monotherapy.

### 3.1. Efficacy compared with placebo

The aim of the three placebo-controlled studies was to compare the efficacy and safety of 2 doses of exenatide (5 and 10 µg) in combination with oral hypoglycaemic treatment with those of a placebo in patients with uncontrolled type-2 diabetes. These were randomised, double-blind studies in which the primary endpoint was change in HbA1c levels after 30 weeks of treatment. Patients were included after a 4-week period on a placebo.

The efficacy and safety of exenatide were evaluated at the dosage of 5 and 10 µg twice a day by subcutaneous injection.

In the 3 studies, patients with type-2 diabetes were inadequately controlled by oral antidiabetic monotherapy (metformin or sulphonylurea, studies 112 and 113) or bitherapy (metformin + sulphonylurea, study 115).

In the exenatide groups, the initial exenatide dosages were 5 µg twice a day for 4 weeks. For patients treated with exenatide 10 µg, this dosage was then increased to 10 µg twice a day.

Inclusion criteria:

- 7.1% ≤ HbA1c ≤ 11.0% in studies 112 and 113
- 7.5% ≤ HbA1c ≤ 11.0% in study 115
- 27 kg/m$^2$ ≤ BMI ≤ 45 kg/m$^2$.

Primary efficacy endpoint common to the 3 studies: change in HbA1c level after 30 weeks of treatment.

Secondary efficacy endpoints considered in this opinion:

- percentage of patients with HbA1c < 7% after 30 weeks of treatment
- patient weight change
- fasting blood glucose level.

In addition, other secondary endpoints were evaluated: interim change in HbA1c level, postprandial blood glucose level, change in islet beta cell function markers. These endpoints are not discussed in this opinion.

These 3 placebo-controlled studies were extended on an open-label basis for the purpose of evaluating the efficacy and safety of exenatide at a dosage of 10 µg twice a day after a further 52 weeks of treatment. The results of these extension periods are not detailed in this opinion.

The results of the placebo-controlled studies are given in Tables 1, 2 and 3, below. These are results of the ITT analysis.

**Efficacy results of the placebo-controlled studies**

**Table 1: study 112**

| | **Study 112 (add-on to metformin)** | | |
|---|---|---|---|
| | **placebo** | **exenatide** | |
| | | **5 µg** | 10 µg |
| **N (ITT)** | 113 | 110 | 113 |
| **Average age (years)** | 53.8 ± 9 | 52.6 ± 11 | 52.4 ± 11 |
| **Mean baseline BMI (kg/m$^2$)** | 34.2 ± 5.92 kg/m$^2$ | | |
| **Mean baseline HbA1c (SD)** | 8.2 ± 0.097% | 8.26 ± 0.107% | 8.18 ± 0.094% |
| **Mean HbA1c change (%) from baseline (SD)** | 0.00 ± 0.106% | - 0.46 ± 0.112%<br>p< 0.01 | - 0.86 ± 0.110%<br>p< 0.01 |
| **BMI < 30 kg/m$^2$** | - 0.45 ± 0.177% (n = 26) | - 1.15 ± 0.171% (n= 33)<br>p< 0.01 | - 1.30 ± 0.170% (n = 30)<br>p< 0.01 |
| **BMI > 30 kg/m$^2$** | + 0.10 ± 0.126% (n =87) | -0.24 ± 0.139% (n = 77)<br>NS | - 0.73 ± 0.137% (n = 83)<br>p< 0.01 |
| **% of patients with HbA1c ≤ 7% at 30 weeks** | 13%<br>(n = 87) | 31.6% (n = 89)<br>p< 0.01 | 46.4% (n = 91)<br>p< 0.01 |
| **Mean weight change (kg) from baseline (SD)** | - 0.2 ± 0.42 | -1.3 ± 0.45<br>p< 0.05 | -2.6 ±0.44<br>p< 0.05 |
| **Mean fasting blood glucose change (mmol/L)** | + 0.79 ± 0.26 | - 0.29 ± 0.28<br>p< 0.05 | - 0.56 ± 0.27<br>p< 0.05 |

**Table 2: study 113**

| | **Study 113 (add-on to sulphonylurea)** | | |
|---|---|---|---|
| | **placebo** | **exenatide** | |
| | | 5 µg | 10 µg |
| **N (ITT)** | 123 | 125 | 129 |
| **Average age (years)** | 54.8 ± 11 | 55.0 ± 10 | 55.9 ± 11 |
| **Mean baseline BMI (kg/m$^2$)** | 33.4 ± 5.60 kg/m$^2$ | | |
| **Mean baseline HbA1c (SD)** | 8.69 ± 0.110% | 8.49 ± 0.101% | 8.61 ± 0.106% |
| **Mean HbA1c change (%) from baseline (SD)** | + 0.06 ± 0.115% | - 0.51 ± 0.111%<br>p< 0.01 | - 0.91 ± 0.110%<br>p< 0.01 |
| **BMI < 30 kg/m$^2$** | + 0.49 ± 0.286% (n = 25) | - 0.62 ± 0.221% (n= 47)<br>p< 0.01 | - 0.87 ± 0.213% (n = 45)<br>p< 0.01 |
| **BMI > 30 kg/m$^2$** | - 0.04 ± 0.124% (n = 98) | -0.41 ± 0.132% (n = 78)<br>p< 0.05 | - 0.90 ± 0.130% (n = 84)<br>p< 0.01 |
| **% of patients with HbA1c ≤ 7% at 30 weeks** | 8.8%<br>(**n** = 68) | 32.6% (n = 86)<br>p< 0.01 | 41.3% (n = 80)<br>p< 0.01 |
| **Mean weight change (kg) from baseline (SD)** | - 0.8 ± 0.32 | -1.1 ± 0.30<br>NS | -1.6 ±0.30<br>p< 0.05 |
| **Mean fasting blood glucose change (mmol/L)** | + 0.32 ± 0.29 | - 0.29 ± 0.28<br>NS | - 0.60 ± 0.28<br>p< 0.05 |

**Table 3: study 115**

| | Study 115 (add-on to metformin + sulphonylurea) | | |
|---|---|---|---|
| | **placebo** | **exenatide** | |
| | | 5 µg | 10 µg |
| **N (ITT)** | 247 | 245 | 241 |
| **Average age (years)** | 55.7 ± 10 | 55.3 ± 9.4 | 54.8 ± 10 |
| **Mean baseline BMI (kg/m$^2$)** | 33.6 ± 5.66 kg/m$^2$ | | |
| **Mean baseline HbA1c (SD)** | 8.49 ± 0.065% | 8.46 ± 0.065% | 8.50 ± 0.068% |
| **Mean HbA1c change (%) from baseline (SD)** | + 0.12 ± 0.079% | - 0.66 ± 0.079%<br>p< 0.01 | - 0.88 ± 0.080%<br>p< 0.01 |
| **BMI < 30 kg/m$^2$** | +0.02 ± 0.135% (n = 71) | - 0.71 ± 0.140% (n= 75)<br>p< 0.01 | - 1.33 ± 0.139% (n = 72)<br>p< 0.01 |
| **BMI > 30 kg/m$^2$** | +0.17 ± 0.095% (n = 176) | - 0.66 ± 0.95% (n = 170)<br>p< 0.01 | - 0.71 ± 0.097% (n = 169)<br>p< 0.01 |
| **% of patients with HbA1c ≤ 7% at 30 weeks** | 9.2%<br>(**n** = 183) | 27.4% (n = 204)<br>p< 0.0001 | 33.5% (n = 186)<br>p< 0.0001 |
| **Mean weight change (kg) from baseline (SD)** | - 0.9 ± 0.21 | -1.6 ± 0.21<br>p< 0.05 | -1.6 **± 0.21**<br>p< 0.05 |
| **Mean fasting blood glucose change (mmol/L)** | + 0.72 ± 0.20 | - 0.60 ± 0.20<br>p< 0.05 | - 0.68 ± 0.20<br>p< 0.05 |

Primary efficacy endpoint: a significant reduction in HbA1c level compared with placebo was observed with exenatide 5 and 10 µg after 30 weeks of treatment.
A dose-efficacy relation was observed: the reduction in HbA1c level was significantly greater in patients treated with exenatide 10 µg than in patients treated with exenatide 5 µg.

Secondary endpoints:

- Evaluation of the change in HbA1c level on each visit showed a slight rise in this level at the end of all 3 placebo-controlled studies in the exenatide arms and in the placebo arms; this increase was not observed during the extension periods in the 3 studies.

- A significant reduction in fasting blood glucose was observed after 30 weeks of treatment with exenatide 5 and 10 µg, compared with placebo.

- Patient weight fell significantly after 30 weeks of treatment with exenatide 5 and 10 µg, compared with placebo. Patients also continued to lose weight during the open-label extension periods.

### 3.2. Efficacy compared with insulin

Three comparison studies were included in the dossier: studies GWAA, GWAD (pivotal Marketing Authorisation studies) and GWAO.

Aims:
The aim of the GWAA and GWAD studies was to evaluate the non-inferiority of the glycaemic control provided by exenatide compared with insulin treatment in patients with uncontrolled type-2 diabetes despite oral bitherapy (metformin + sulphonylurea).

The aim of the GWAO study was to evaluate the non-inferiority of the blood glucose control provided by exenatide compared with insulin treatment in patients with uncontrolled type-2 diabetes despite oral monotherapy (metformin or sulphonylurea).

Non-inferiority was demonstrated if the upper CI 95% limit of the difference in HbA1c change between the insulin and exenatide groups (exenatide minus insulin) was less than 0.4%.

Methodology:
The studies were randomised open-label studies, in parallel groups (GWAA and GWAD) or crossover (GWAO).
There was no 'washout' period between the exenatide treatment sequences and the insulin treatment sequence in the GWAO study.

The efficacy and safety of exenatide administered twice a day subcutaneously were compared with those of insulin glargine (Lantus, GWAA and GWAO) and biphasic insulin aspart (Novomix 30, GWAD).

In the exenatide groups, the initial exenatide dosage was 5 µg twice a day for 4 weeks, after which it was increased to 10 µg twice a day.

In the GWAA study: insulin glargine was commenced at a dosage of 10 IU/day in one daily injection, with a 2 IU forced titration to target a fasting blood glucose level of less than 5.6 mmol/l for three consecutive days with no hypoglycaemic episode.

In the GWAD study: biphasic insulin aspart was administered in 2 daily injections with titration to target a fasting blood glucose level of less than 7 mmol/l and a postprandial blood glucose level of less than 10 mmol/l (2 hours after a meal), with no hypoglycaemic episode.

In the GWAO study: insulin glargine was commenced at a dosage of 10 IU/day in one daily injection, with a stepwise forced titration of 2 to 8 IU/week to target a fasting blood glucose level of less than 5.6 mmol/l with no hypoglycaemic episode.

The 3 studies included patients with type-2 diabetes inadequately controlled by oral bitherapy or monotherapy (metformin and/or sulphonylurea) at the maximum tolerated dose.

Inclusion criteria:
- 7% ≤ HbA1c ≤ 10.0% and 25 kg/m$^2$ ≤ BMI ≤ 45 kg/m$^2$ in the GWAA study
- 7% ≤ HbA1c ≤ 11.0% and 25 kg/m$^2$ ≤ BMI ≤ 40 kg/m$^2$ in the GWAD study
- 7.1% ≤ HbA1c ≤ 11.0% and 25 kg/m$^2$ ≤ BMI ≤ 40 kg/m$^2$ in the GWAO study.

Patients with a history of more than 3 episodes of severe hypoglycaemia[1] in the 6 months prior to the beginning of the studies were not included.

**Primary efficacy endpoint common to the 3 studies:** change in HbA1c level after 26 weeks of treatment (GWAA study), 52 weeks of treatment (GWAD study) or 16 weeks of treatment (GWAO study).

Secondary efficacy endpoints considered in this opinion:
- percentage of patients with HbA1c < 7%
- weight change
- fasting blood glucose level.

In addition, other secondary endpoints were evaluated: interim change in HbA1c level, change in islet beta cell function markers, blood glucose self-monitoring measures, change in lipid profile, and quality of life. These endpoints are not discussed in this opinion.

The results of these non-inferiority studies are given in Tables 4, 5 and 6, below. The results shown are from the per-protocol analysis.

[1] *An episode of hypoglycaemia was defined by blood glucose < 3.4 mmol/l or 3.3 mmol/l, depending on the study.*
*An episode of severe hypoglycaemia was defined as:*
*- a symptomatic episode of hypoglycaemia requiring the intervention of another person, and*
*- blood glucose < 2.8 mmol/l or effective treatment with either an oral carbohydrate or glucagon or glucose administered intravenously.*

## Efficacy results of the insulin comparison studies

**Table 4: GWAA study**

| | GWAA study (add-on to metformin + sulphonylurea) | |
|---|---|---|
| | **Insulin glargine** | **Exenatide** |
| **Mean dose at end of study** | 24.9 IU/day | 10 µg x 2/day |
| **N (Per Protocol)** | 227 | 228 |
| **Mean age (years)** | 58.0 ± 9.5 | 59.8 ± 8.8 |
| **Mean baseline BMI (kg/m$^2$)** | 31 kg/m$^2$ | |
| **Mean baseline weight (kg)** | 89.45 ± 1.34 | 88.7 ± 1.35 |
| **Mean baseline HbA1c (SD)** | 8.24 ± 0.08% | 8.21 ± 0.08% |
| **Mean HbA1c change (%) from baseline (SD)** | -1.10% ± 0.07% | - 1.13% ± 0.07% |
| **CI 95% of difference at 26 weeks** | [- 0.18; 0.13]<br>p = 0.7398 | |
| **% of patients with HbA1c ≤ 7% at 26 weeks** | 49.3% | 48.8% |
| **Mean weight change (kg) from baseline (SD)** | + 1.85 ± 0.23 | - 1.92 ± 0.22 |
| **CI 95% of difference in weight at 26 weeks** | - 4.04<br>[ - 4.61; - 3.46] | |
| **Mean fasting blood glucose change (mmol/L)** | - 2.86 ± 0.21 | - 1.34 ± 0.19 |
| **CI 95% of difference in fasting blood glucose at 26 weeks** | 1.52<br>[1.05; 1.99] | |
| **Change in postprandial blood glucose excursions (mmol/l)**<br>**- morning**<br>**- midday**<br>**- evening** | <br>-0.22 ± 0.170<br>+0.28 ± 0.166<br>+0.11 ± 0.190 | <br>-2.58 ± 0.172<br>-0.08 ± 0.168<br>-1.91 ± 0.192 |

**Table 5: GWAD study**

| | GWAD study (add-on to metformin + sulphonylurea) | |
|---|---|---|
| | **Biphasic insulin aspart** | **Exenatide** |
| **Mean dose at end of study** | 24.4 IU/day | 10 µg x 2/day |
| **N (Per Protocol)** | 224 | 222 |
| **Average age (years)** | 58.5 ± 9.2 | 58.8 ± 8.7 |
| **Mean baseline BMI (kg/m$^2$)** | 30.5 kg/m$^2$ | |
| **Mean baseline weight (kg)** | 84.1 ± 1.01 | 85.9 ± 1.02 |
| **Mean baseline HbA1c (SD)** | 8.67 ± 1.05% | 8.60 ± 1.04% |
| **Mean HbA1c change (%) from baseline (SD)** | - 0.86% ± 0.08% | - 1.01% ± 0.08% |
| **CI 95% of difference at 52 weeks** | [- 0.33; 0.04]<br>p = 0.1273 | |
| **% of patients with HbA1c ≤ 7% at 52 weeks** | 24.1% | 33.2% |
| **Mean weight change (kg) from baseline (SD)** | + 2.89 ± 0.18 | - 2.51 ± 0.18 |
| **CI 95% of difference in weight at 52 weeks** | - 5.20<br>[- 5.81; - 4.59] | |
| **Mean fasting blood glucose change (mmol/L)** | - 1.57 ± 0.20 | - 1.68 ± 0.20 |
| **CI 95% of difference in fasting blood glucose at 52 weeks** | - 0.11<br>[-0.61; 0.38] | |
| **Change in postprandial blood glucose excursions (mmol/l)**<br>**- morning**<br>**- midday**<br>**- evening** | <br>-1.30 ± 0.16<br>+0.46 ± 0.17<br>-0.66 ± 0.19 | <br>-2.74 ± 0.16<br>-0.20 ± 0.17<br>-1.97 ± 0.18 |

**Table 6: GWAO study**

| | GWAO study (add-on to metformin or sulphonylurea) | |
|---|---|---|
| | **Insulin glargine** | **Exenatide** |
| **Mean dose at end of study** | 27.3 IU/day | 10 µg x 2/day |
| **N (Per Protocol)** | 59 | 55 |
| **Average age (years)** | 54.5 ± 9.4 | 54.1 ± 8.5 |
| **Mean baseline weight (kg)** | 84.13 ± | 88.07 ± |
| **Mean baseline BMI (kg/m$^2$)** | 31.27 kg/m$^2$ | |
| **Mean baseline HbA1c (SD)** | 8.91 ± 1.12% | 8.95 ± 1.05% |
| **Mean HbA1c change (%) from baseline (SD)** | - 1.41% ± 0.09% | - 1.43% ± 0.09% |
| **CI 95% of difference at 16 weeks** | [- 0.20; 0.15]<br>p = 0.7728 | |
| **% of patients with HbA1c ≤ 7% at 16 weeks** | 41.1% | 40.2% |
| **Mean weight change (kg) from baseline (SD)** | + 0.35 ± 0.36 | - 1.95 ± 0.36 |
| **CI 95% of difference in weight at 16 weeks** | - 2.30<br>[- 2.91; -1.70] | |
| **Mean fasting blood glucose change (mmol/L)** | - 4.17 ± 0.23 | - 3.04 ± 0.23 |
| **CI 95% of difference in fasting blood glucose at 16 weeks** | 1.13<br>[0.61; 1.65] | |

Primary efficacy endpoint: in all these studies, the efficacy of exenatide was significantly non-inferior to that of insulin in lowering HbA1c.

Secondary endpoints:

- Evaluation of HbA1c level at each visit showed a reduction in the efficacy of exenatide over time: a slight increase in HbA1c level appeared at the end of all 3 studies in both treatment arms.
- In the GWAA and GWAO studies, the percentage of patients achieving HbA1c level ≤ 7% was comparable between the insulin glargine and exenatide groups.
- Patients treated with exenatide lost weight during the studies, whereas patients treated with insulin put on weight. The difference in weight change between the two treatment groups was significant.
- A negative correlation was revealed between change in HbA1c level and weight change in patients treated with insulin:
  r = -0.10 (GWAA); r = -0.2 (GWAD).
- A positive correlation was revealed between change in HbA1c level and weight change in patients treated with exenatide:
  r = 0.24 (GWAA); r = 0.36 (GWAD).

The ITT analysis results confirmed the per-protocol results.

## 3.3. Adverse effects

### 3.3.1. General adverse effects

During the 5 clinical trials evaluated by the registration authorities, the most frequently observed adverse events were hypoglycaemia and nausea/vomiting:

- Hypoglycaemia:

- The studies on patients treated with exenatide and a hypoglycaemic sulphonylurea (with or without metformin) showed that the incidence of hypoglycaemia was raised compared with placebo (23.5% and 25.2% against 12.6% and 3.3%).
- 4.9% of patients treated with exenatide in combination with metformin had hypoglycaemia against 5.3% on placebo.
- The frequency of hypoglycaemia was the same in the groups of patients treated with insulin and the groups of patients treated with exenatide (56% against 54%).

In the GWAA study, 8 episodes of severe hypoglycaemia were observed: 4 in the insulin group (1.8%) and 4 in the exenatide group (1.8%), compared with none in the GWAD study. Nocturnal hypoglycaemia was less frequent in the exenatide groups than in the insulin groups.

**Table 7: Hypoglycemia in GWAA and GWAD studies**

| | **GWAA** | | **GWAD** | |
|---|---|---|---|---|
| | **Insulin glargine N=267** | **exenatide N=282** | **Biphasic insulin aspart N=248** | **exenatide N=253** |
| **All hypoglycaemia** | 59.9% | 55.6% | 53.0% | 51.6% |
| **Severe hypoglycaemia*** | 1.8% | 1.8% | 0% | 0% |
| **Nocturnal hypoglycaemia** | 35.2% | 16.7% | 25.0% | 17.4% |

** - an episode of severe hypoglycaemia was defined as:*
*a symptomatic episode of hypoglycaemia requiring the intervention of another person, and blood glucose < 2.8 mmol/l or effective treatment with either an oral carbohydrate, or glucagon, or glucose administered intravenously.*

- Nausea:

In the exenatide groups, 50% of patients had nausea. The frequency and intensity of patients' nausea diminished during the course of treatment.

- Injection site reactions:

Injection site reactions were reported in approximately 5.1% of patients treated with exenatide. These reactions were generally mild in intensity and did not lead to the suspension of treatment.

- Early discontinuation of treatment:

In the GWAA and GWAD studies, 19.4% and 22% of patients treated with exenatide stopped treatment during the study, compared with 9.7% and 10.8% of patients treated with insulin. The main reason for stopping exenatide treatment was an adverse event.
Discontinuations following adverse events were as follows:
- 9% of exenatide-treated patients, including 168 out of 2,997 patients who stopped treatment after functional gastrointestinal disorders, especially nausea, and 5 out of 2,997 (< 1%) who stopped treatment after hypoglycaemia
- 1% of insulin-treated patients
- 3% of patients given placebo.

GWAO study:
Approximately 53% of patients had adverse events attributed to insulin, compared with 66% in the exenatide group.
Nausea was the most frequently observed adverse event in exenatide-treated patients (**33.3%** in the exenatide group against 3.9% in the insulin group).
The frequency of hypoglycaemia was the same in insulin-treated patients and exenatide-treated patients.
In the insulin group, 8 episodes of severe nocturnal hypoglycaemia were observed in 3 patients.
No severe hypoglycaemic episode was observed in the exenatide group.

**Table 8: Hypoglycemia in GWAO study**

| | **GWAO** | | | |
|---|---|---|---|---|
| | **In combination with metformin** | | **In combination with a sulphonylurea** | |
| | **Insulin glargine N = 69** | **Exenatide N = 76** | **Insulin glargine N = 58** | **Exenatide N = 60** |
| **All hypoglycaemia** | 17.4 % | 2.6 % | 34.5 % | 30.0 % |
| **Nocturnal hypoglycaemia** | 13.0 % | 1.3 % | 15.5 % | 6.7 % |

### 3.3.2. Immunogenicity

In the 3 placebo-controlled studies:
- 38% of patients had low anti-exenatide antibody levels at 30 weeks. Glycaemic control (HbA1c) was generally comparable to that of patients not presenting antibodies.
- 6% of patients had higher levels of anti-exenatide antibodies at 30 weeks. Half of these patients experienced no decrease in their HbA1c level.

In the insulin comparison studies, 40% of exenatide patients had anti-exenatide antibodies. Efficacy and adverse events were comparable among exenatide-treated patients regardless of the anti-exenatide antibody level observed.

In the GWAO study, 39% of patients had anti-exenatide antibodies. This percentage is comparable to that observed in the GWAA and GWAD studies.

### 3.4. Conclusions

The placebo-controlled studies showed the efficacy of exenatide in lowering HbA1c levels. The reduction was in the order of 1%.

The per-protocol analysis of the insulin comparison studies demonstrated the non-inferiority of blood glucose control by exenatide in type-2 diabetic patients compared with insulin. This analysis was confirmed by the ITT analysis.
The investigators prescribed the insulins at low doses. This bias seems to be linked to the open-label nature of the studies.

All the studies showed weight loss in exenatide-treated patients; this loss was observed irrespective of whether they had nausea.
The reduction in HbA1c level was the same whatever the patients' BMI.
Patients who did not lose weight had a smaller reduction in HbA1c than patients who did lose weight.
The percentages of hypoglycaemia were comparable between the two groups of patients (exenatide 54%, insulin 56%) but the distribution of the types of hypoglycaemia was not the same: nocturnal hypoglycaemias were less frequent with exenatide than with insulin, but in contrast more diurnal hypoglycaemias were observed with exenatide than with insulin. In addition, postprandial hyperglycaemias were less frequent in exenatide-treated patients than in insulin-treated patients.
It should be noted, however, that patients who had a history of more than three episodes of severe hypoglycaemia in the 6 months prior to the beginning of the studies were ineligible for inclusion in the studies.
The Committee regrets that no French patients were included in these studies.

# 4 TRANSPARENCY COMMITTEE CONCLUSIONS

## 4.1. Actual benefit

Type-2 diabetes is a chronic disease with potentially serious complications.
BYETTA is used in the context of treatment for hyperglycaemia.

The efficacy/adverse effects ratio for BYETTA is high.

Alternative medicinal products exist.

BYETTA is an adjunctive therapy for the management of type-2 diabetic patients.

Public health benefit:

The public health burden due to type-2 diabetes is considerable. That corresponding to the subpopulation of patients likely to benefit from BYETTA is moderate.

Improving the therapeutic management of type-2 diabetics is a public health need.

In patients inadequately controlled by monotherapy, in the absence of a comparison with an oral bitherapy (which would avoid the need for injections), the expected impact of BYETTA on glycaemic control and on diabetes-associated morbimortality cannot be evaluated.

In patients inadequately controlled by oral bitherapy, the expected impact is not directly quantifiable in the absence of a demonstration of its effects on morbimortality and of long-term data on HbA1c balance in patients treated with BYETTA in combination with two oral antidiabetics (OADs), compared with a combination of two OADs and insulin or a glitazone. 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 obese type-2 diabetic patients (BMI ≥ 30). The fact that there is no titration with BYETTA and the use of a fixed dose mean that a positive impact may be expected in patients whose HbA1c is inadequately controlled by insulin because of a non-optimal titration for fear of hypoglycaemia.

There is also no guarantee that experimental data can be transposed into clinical use, particularly because:

- compliance with BYETTA, a treatment requiring two injections a day and frequently causing disorders of gastrointestinal function, is not assured;
- no French patients were included in the multi-centre trials. The characteristics of the population studied are appreciably different from the diabetic population in France (the trial population was younger, with a higher BMI and different eating habits).

As a result, in view of the available data, it is not expected that BYETTA will benefit public health in cases of failure with oral monotherapy. It is expected that this product will provide a low public health benefit in cases of failure with oral bitherapy.

The actual benefit of BYETTA is substantial.

## 4.2. Improvement in actual benefit

BYETTA provides a minor improvement in actual benefit (IAB IV) in the management of type-2 diabetes in patients treated with a combination of metformin and hypoglycaemic sulphonylurea who have not achieved adequate blood glucose control at the highest tolerated doses of these treatments.

## 4.3. Therapeutic use

The objectives of therapy are:

- glycaemic control: control of HbA1c
- control of associated risk factors.

According to the guideline on 'Medical treatment of type-2 diabetes', published by AFSSAPS and HAS in November 2006, initial treatment for type-2 diabetes is based on the evaluation of and realistic changes to lifestyle (diet and exercise). Active steps to combat a sedentary lifestyle as well as dietary planning are essential measures at all stages in the management of this disease.

The practitioner may resort to using oral antidiabetics when dietary and lifestyle measures (DLM) alone are not enough to control blood glucose levels: HbA1c > 6 %. There are 4 drug categories: metformin, intestinal alpha-glucosidase inhibitors (AGIs), insulin secretors, and glitazone.

The different treatment stages are summarised in the following table.

**Table 9: Treatment strategy (long-term condition 8 – Type-2 diabetes)**

| Initial HbA1c | Treatment | Target HbA1c |
|---|---|---|
| HbA1c between 6% and 6.5% despite DLM | Monotherapy with metformin (or AGIs in the event of intolerance or contraindication) | < 6.5 % |
| HbA1c > 6.5% despite DLM | Monotherapy with metformin or insulin secretor or AGIs | Maintain HbA1c < 6.5% |
| HbA1c > 6.5% despite monotherapy and DLM | Bitherapy | Reduce HbA1c < 6.5% |
| HbA1c > 7% despite bitherapy and DLM | Tritherapy: metformin + insulin secretor + glitazone or insulin + metformin **±** other OADs except glitazone | Reduce HbA1c < 7% |
| HbA1c > 8% despite tritherapy and DLM | Insulin + metformin **±** other OADs except glitazone | Reduce HbA1c < 7% |

DLM: Diet and lifestyle measures; OADs: oral antidiabetics; AGIs: intestinal alpha-glucosidase inhibitors

The Committee considers that BYETTA in its therapeutic indication should be used in type-2 diabetes patients treated with a combination of metformin and hypoglycaemic sulphonylurea who have not achieved adequate blood glucose control at the highest tolerated doses of these treatments.

[2] Diabetes management: Type 2 diabetes. Doctor's guide – Long-Term Condition, HAS – May 2006

BYETTA could then be an alternative to the addition of a glitazone in tritherapy or it could postpone the use of insulin.
The acceptability of this injection treatment and the optimal duration of treatment, with the potential occurrence of therapeutic escape, have yet to be determined.

### 4.4. Target population

According to the indication in the Marketing Authorisation (MA), the BYETTA target population is type-2 diabetes patients treated with metformin and/or a hypoglycaemic sulphonylurea who have not achieved adequate glycaemic control at the maximum tolerated doses of these medications. It consists of 2 subpopulations:

- patients for whom properly administered oral metformin and sulphonylurea bitherapy at the maximum tolerated dose has failed (HbA1c > 7%)
- patients for whom properly administered oral metformin or sulphonylurea monotherapy at the maximum tolerated dose has failed (HbA1c > 6,5%)

According to the *BEH* (weekly epidemiological bulletin, InVS, March 2006), the number of diabetic patients treated in 2006 was between 2,037,000 and 2,166,000.
Of those, 91% are type-2 diabetics (ENTRED study, 2001-2003 – *Réseaux Diabète* N° 29 – September 2006).
According to the partially published results of the ECODIA-2 study (*Réseaux Diabète* No 31 – March 2007), 83.2% of type 2 diabetics are treated with an oral antidiabetic without insulin; of these, 24.6% are treated with metformin + sulphonylurea bitherapy, 24% with biguanide monotherapy and 21.6% with sulphonylurea monotherapy.
The ECODIA-2 data indicate that 68% of the patients have an HbA1c level above 6.5%, and 51.5% have an HbA1c level above 7%.
On these bases, the number of patients for whom properly administered oral metformin and sulphonylurea bitherapy at the maximum tolerated dose has failed is between 195,000 and 208,000 patients and the number for whom properly administered oral metformin or sulphonylurea monotherapy has failed is between 478,000 and 509,000 patients.
The target population for BYETTA corresponding to the indications in the MA is therefore in the order of 673,000 to 717,000 patients.

The population of patients most in a position to benefit from BYETTA, i.e. the target population for improvement in actual benefit, consists of patients treated with a combination of metformin and hypoglycaemic sulphonylurea who have not achieved adequate blood glucose control at the highest tolerated doses of these medicines, and is in the order of 195,000 to 208,000 patients.

### 4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indications and at the posology given in the Marketing Authorisation.

The Transparency Committee requests that a study be set up on a representative sample of French type-2 diabetes patients treated with BYETTA. 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 for use of this product (indication, posology and dosage adaptations, concomitant treatments, blood glucose monitoring procedures, etc.)
- the compliance rate for the treatment
- the frequency of discontinuations and the reasons for them
- the change in HbA1c and weight, and the occurrence of hypoglycaemic episodes~~,~~ in the long term (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%