HAUTE AUTORITÉ DE SANTÉ

DIABETOLOGY
New indication
November 2014

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

BYETTA (exenatide), antidiabetic

No clinical benefit demonstrated in combination with a basal insulin and metformin

Main points

- BYETTA has Marketing Authorisation in triple therapy, in combination with a basal insulin and metformin in adults who have not achieved adequate glycaemic control with these medicinal products in triple therapy.
- This use is set down in a specialist opinion justifying the escalation of treatment for the management of type 2 diabetes.

Pre-existing indications

- BYETTA is indicated for the treatment of type 2 diabetes mellitus in combination with metformin, sulfonylureas, thiazolidinediones, metformin and a sulfonylurea, metformin and a thiazolidinedione, in adults who have not achieved adequate glycaemic control on maximally tolerated oral doses of these oral therapies.
- This summary does not cover these indications.

Therapeutic use

- The generally recommended use is first of all monotherapy with metformin, then dual therapy with the combination of metformin and a sulfonylurea.
  If the glycaemic target is not achieved despite dual therapy with metformin and a sulfonylurea, the use of GLP-1 analogues can be considered only in certain special situations: if the difference from the HbA1c target is > 1%, add insulin in combination with metformin + sulfonylurea or add a GLP-1 analogue in triple therapy, if BMI is ≥ 30 kg/m^2 or if weight gain on insulin gives cause for concern.
- **Role of the medicinal product in the therapeutic strategy**
  The BYETTA proprietary medicinal products are a treatment alternative to fast-acting insulin when initiating treatment comprising basal insulin and metformin at an optimal dose in patients with type 2 diabetes who are not adequately controlled by these medicinal products, who are intolerant to or have a contraindication to the use of sulfonylurea or in whom triple therapy with insulin/metformin/sulfonylurea has failed.
  Appropriate titration intended to normalise fasting blood glucose must previously have been given.

Clinical data

- An open randomised study evaluated the non-inferiority of exenatide by comparison with insulin lispro in patients with type 2 diabetes not controlled by insulin glargine (at a high dose > 60 IU/day) and metformin (2 g/day on average) with an HbA1c of between 7 and 10%. The study provided for a 12-week titration phase before randomisation. The per protocol population consisted of 510 patients (i.e. 80.1% of the patients randomised): 247 patients to the exenatide group and 263 to the insulin lispro group. At 30 weeks, the dose of insulin glargine was 56.9 IU/day in the exenatide group and 93.7 IU/day in the insulin lispro group. Non-inferiority between the combination insulin glargine/metformin/exenatide and the combination insulin glargine/metformin/insulin lispro was demonstrated at 30 weeks in the per protocol population, in terms of the change in the HbA1c level by comparison with the level on inclusion.
  These results were confirmed in the intention-to-treat population. The patients in the exenatide group lost weight, whereas those in the insulin lispro group gained weight (secondary endpoint).

- The proportion of patients with an adverse event linked to the treatment was larger in the exenatide group (72.4%, n = 228) than in the insulin lispro group (56.1%, n = 175). The gastrointestinal adverse effects (nausea, vomiting,

diarrhoea) were more common in the exenatide group (47% versus 13%). Hypoglycaemic episodes were less common in the exenatide group (29.5% versus 41.7% of patients) as were confirmed diurnal hypoglycaemic episodes (15.2% versus 33.7%). The numbers of nocturnal hypoglycaemic episodes were similar (24.8 versus 26.6%) and 22.2% of patients (n = 70) developed anti-exenatide antibodies in the exenatide group.

Benefit of the medicinal product

- The actual benefit* of BYETTA is substantial.
- In combination with basal insulin and metformin in patients with type 2 diabetes inadequately controlled by these medicinal products, on the basis of the available data, i.e. a non-inferiority study of exenatide versus insulin lispro, BYETTA does not provide any clinical added value** (CAV V, none).
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 05 November 2014 (CT-12888) and is available at **www.has-sante.fr**

[i] * The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement by the National Health Insurance.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value".