HAUTE AUTORITÉ DE SANTÉ

DIABETOLOGY
New medicinal product
February 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

OZEMPIC (semaglutide), antidiabetic agent

High clinical benefit in combination with metformin with or without a sulphonylurea, but no clinical added value in the management of patients with type 2 diabetes

Insufficient clinical benefit to justify reimbursement as monotherapy, as dual therapy with sulphonylurea and basal insulin, and as triple therapy with metformin and basal insulin, in patients with type 2 diabetes

Main points

- OZEMPIC, a GLP-1 analogue, has an MA for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise: as monotherapy when metformin is considered inappropriate due to intolerance or contraindications, in addition to other medicinal products for the treatment of diabetes.
- Considering the efficacy data on an interim endpoint, the variation in HbA1c, and in the absence of data demonstrating a reduction in the risk of morbidity and mortality, OZEMPIC is an additional alternative as dual therapy with metformin and as triple therapy with metformin and a sulphonylurea.
- In the absence of robust and relevant data as monotherapy, as dual therapy with sulphonylurea and basal insulin, and as triple therapy with metformin and basal insulin, OZEMPIC is not recommended in these stages of the therapeutic strategy.
- OZEMPIC has a similar safety profile to other GLP-1 analogues.

Therapeutic strategy

- Diabetes is an evolving disease and treatment must therefore be regularly reassessed in all its components: lifestyle and dietary measures, patient education and medicinal treatment.
- The target blood glucose level for patients with type 2 diabetes should be defined for each patient on the basis of their comorbidities and life expectancy: the HbA1c target ranges from 6.5% to 8%. An HbA1c target of less than or equal to 7% is recommended for the majority of patients. Medicinal treatment should be initiated or reassessed if HbA1c is greater than 7% despite compliance with lifestyle and dietary measures.
- The strategy generally recommended is as follows: monotherapy with metformin, then, in the event of failure, dual therapy with a combination of metformin + sulphonylurea.
- If target blood glucose levels are not obtained under dual therapy with metformin + sulphonylurea:
  - if the difference with respect to the target is < 1% HbA1c: triple therapy with metformin + sulphonylurea + alpha-glucosidase inhibitors or DPP-4 inhibitors.
  - if the difference with respect to the target is > 1% HbA1c: triple therapy with insulin + metformin + sulphonylurea.

Role of the medicinal product in the therapeutic strategy

OZEMPIC is an additional alternative when the BMI is ≥ 30 kg/m^2 or weight gain under treatment with insulin or the occurrence of hypoglycaemic episodes are of concern:

- as dual therapy with metformin, in the event of intolerance or contraindication to sulphonylureas, and the difference from the target is > 1% HbA1c despite monotherapy with metformin,
- as triple therapy with metformin and a sulphonylurea, in the event of failure of dual therapy with metformin/sulphonylurea with a difference from HbA1c target of > 1%, or oral triple therapy including metformin + sulphonylurea.

Clinical data

- Two studies demonstrated the superiority of semaglutide as dual therapy with metformin on an interim endpoint, variation in HbA1c, with an effect size:
  - of -0.4% compared to dulaglutide at 40 weeks (open-label study)
  - of -1.1% compared to sitagliptin at 56 weeks (double-blind study)
- Two open-label studies demonstrated the overall superiority of semaglutide on HbA1c variation, for patients receiving dual therapy with metformin or triple therapy with metformin/sulphonylurea, and with an overall effect size:
  - of between -0.4% and -0.8% compared to insulin glargine at 30 weeks;
  - of -0.6% compared to exenatide ER 2 mg at 56 weeks (study having evaluated the 1 mg dose of semaglutide only).
- No data are available concerning semaglutide as monotherapy in the context of the MA in patients with a contraindication or intolerance to metformin.
- No data are available concerning semaglutide in combination with insulin therapy versus a relevant comparator. A double-blind study having demonstrated the superiority of semaglutide in combination with basal insulin and metformin, on HbA1c variation, compared to placebo (irrelevant comparator).
- An open-label study having included patients with type 2 diabetes and at high cardiovascular risk demonstrated that semaglutide does not result in excess events compared to placebo.

Benefit of the medicinal product

- The actual clinical benefit* of OZEMPIC is
  - high: as dual therapy in combination with metformin, as triple therapy in combination with metformin and a sulphonylurea;
  - insufficient to justify its reimbursement by public funding: as monotherapy, as dual therapy in combination with a sulphonylurea, as dual therapy in combination with basal insulin, as triple therapy in combination with metformin and basal insulin.
- OZEMPIC does not provide any clinical added value** (CAV V) in combination with metformin (dual therapy) or in combination with metformin and a sulphonylurea (triple therapy) in the management of patients with type 2 diabetes.
- Approved for non-hospital pharmacy reimbursement or for hospital treatment as dual therapy in combination with metformin, as triple therapy in combination with metformin and a sulphonylurea.

HAUTE AUTORITÉ DE SANTÉ
This document was drafted on the basis of the Transparency Committee opinion dated 20 February 2019 (CT-17176)
available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a 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 ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) corresponds to the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV level from I, major, to IV, minor. A level V CAV (equivalent to "no clinical added value") denotes a "lack of clinical improvement".