HAUTE AUTORITÉ DE SANTÉ

DIABETOLOGY
New medicinal product
October 2014

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

VIPIDIA (alogliptin) and **VIPDOMET** (alogliptin/metformin), antidiabetics

No clinical benefit demonstrated in the management of patients with type 2 diabetes

Main points

- **VIPIDIA** has Marketing Authorisation in the treatment of type 2 diabetes in combination with other blood glucose-lowering medicines, including insulin, when these, combined with diet and exercise, do not provide adequate glycaemic control.
- Its efficacy has been demonstrated in patients inadequately controlled in dual therapy with metformin or a sulfonylurea and in triple therapy with insulin and metformin.
- **VIPDOMET** has Marketing Authorisation in the treatment of type 2 diabetes:
  - in adult patients inadequately controlled by the maximum tolerated dose of metformin in monotherapy, or in those already receiving an alogliptin-metformin combination.
  - in combination with pioglitazone in adult patients inadequately controlled by the maximum tolerated dose of metformin and pioglitazone.
  - in combination with insulin in patients for whom a stable dose of insulin and metformin alone is not sufficient to provide adequate glycaemic control.
- The fixed-dose combination of alogliptin/metformin has not shown any clinical added value compared with the free combination of alogliptin and metformin.

Therapeutic use

- The therapeutic strategy generally recommended is to start with a monotherapy with metformin. If the glycaemic target is not achieved and there is a contraindication to one of the substances, switching to dual therapy combining metformin and sulfonylurea, then triple therapy combining metformin, sulfonylurea and a gliptin, or an alpha-glucosidase inhibitor, is recommended.
- The oral antidiabetic treatments recommended in combination with insulin therapy are generally metformin and sulfonylureas.

Role of the medicinal product in the therapeutic strategy

VIPIDIA is an additional medicine used in inadequately controlled type 2 diabetes:
- in dual therapy in combination with metformin, in cases of intolerance or contraindication to sulfonylureas,
- in dual therapy in combination with a sulfonylurea, in cases of intolerance or a contraindication to metformin,
- in triple therapy in combination with metformin and insulin.

VIPDOMET can be used in patients not controlled by metformin in monotherapy at the maximum tolerated dose, or as a replacement for the free combination of alogliptin-metformin in this indication, and in combination with insulin as part of a triple therapy.

Clinical data

- The efficacy of alogliptin 25 mg has been evaluated in four phase III studies with the change in the HbA1c level as primary efficacy endpoint.
- In dual therapy with metformin, alogliptin 25 mg was superior to placebo at 26 weeks with a difference between the groups of -0.5% in HbA1c in a study that included 527 patients.
- In dual therapy with metformin, alogliptin was not inferior, in terms of the change in the HbA1c level, to glipizide at 104 weeks, in a study that included 2638 patients.
- In dual therapy with glibenclamide, alogliptin was superior to placebo (difference of -0.5%) at 26 weeks in a study that included 500 patients. More than 50% dropouts were observed.
- In combination with insulin and metformin, a subgroup analysis (n = 150 patients) showed the superiority of alogliptin versus placebo (intergroup difference of -0.6%).
- The most frequent adverse events were hypoglycaemic episodes, diarrhoea and nausea. A cardiovascular safety study showed the non-inferiority of alogliptin compared with placebo as regards the occurrence of major cardiovascular events over a median follow-up period of 19 months.
- Bioequivalence between the fixed-dose combination alogliptin/metformin and the separate use of each of the active substances has been established. No phase III study has been performed with the fixed-dose combination. The available efficacy data are from studies that evaluated alogliptin (VIPIDIA).

Benefit of the medicinal product

- The actual benefit* of VIPIDIA is:
  - substantial as dual therapy in combination with metformin,
  - substantial in dual therapy in combination with a sulfonylurea,
  - insufficient in dual therapy in combination with insulin,
  - insufficient in triple therapy in combination with metformin and a sulfonylurea,
  - moderate in triple therapy in combination with metformin and insulin.
- In the indications in which the actual benefit is moderate or substantial, given the absence of demonstrated superiority by comparison with the available oral antidiabetics, and the absence of data on long-term safety, VIPIDIA does not provide any clinical added value** (CAV V, none) in the management of patients with type 2 diabetes who are inadequately controlled, in dual oral therapy in combination with metformin or a sulfonylurea, and in triple therapy in combination with metformin and insulin.
- The actual benefit* of VIPOMET is:
  - substantial as an adjunct to diet and exercise in improving glycaemic control in adult patients insufficiently controlled by the maximum tolerated dose of metformin in monotherapy, or those already receiving a free combination of alogliptin and metformin.
  - moderate in combination with insulin (i.e. in triple therapy) as an adjunct to diet and exercise in improving glycaemic control in patients when a stable dose of insulin and metformin alone are not sufficient to provide adequate glycaemic control.
  - in combination with pioglitazone: the Committee cannot give a ruling on this obsolete indication, since pioglitazone is no longer on the market.
- Given the absence of any demonstrated clinical added value of the fixed-dose combination by comparison with the free combination of metformin and alogliptin or of other oral antidiabetics, VIPDOMET does not provide any clinical added value** (CAV V, none) in the management of type 2 diabetic patients whose treatment includes the free combination of alogliptin and metformin or indeed in triple therapy in patients insufficiently controlled by the maximum dose of metformin combined with an insulin.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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[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 for hospital use.

** 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".