HAUTE AUTORITÉ DE SANTÉ

DIABETOLOGY
New medicinal product
November 2014

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

INVOKANA (canagliflozin) and **VOKANAMET** (canagliflozin/metformin), antidiabetics

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

Main points

- **INVOKANA** has Marketing Authorisation in the treatment of type 2 diabetes:
  - in monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance or a contraindication.
  - in combination with other blood glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.
- Its efficacy has been demonstrated in patients insufficiently controlled in dual therapy with metformin, in triple therapy with metformin and a sulfonylurea and in triple therapy with insulin and metformin.
- Because of its diuretic mechanism of action, caution is recommended in patients for whom a drop in blood pressure could constitute a risk.
- **VOKANAMET** has Marketing Authorisation in the treatment of type 2 diabetes:
  - in patients not adequately controlled by metformin alone at the maximum tolerated dose.
  - in patients who have insufficient glycaemic control at the maximum dose of metformin combined with other blood glucose-lowering medicines including insulin.
  - in patients already being treated with the combination of canagliflozin and metformin as separate tablets.
- The fixed-dose combination of canagliflozin/metformin has not shown any clinical benefit by comparison with the free combination of canagliflozin and metformin.

Therapeutic use

- The generally recommended use is first of all 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

INVOKANA is an additional medicine used in insufficiently controlled type 2 diabetes:
- in dual therapy in combination with metformin, from among the oral antidiabetics available, in cases of intolerance or contraindication to sulfonylureas.
- in triple therapy in combination with metformin and sulfonylureas, from among the recommended oral antidiabetics available,
- in triple therapy in combination with metformin and insulin.

VOKANAMET can be used in patients insufficiently controlled by metformin alone at the maximum tolerated dose, or in combination with a sulfonylurea or with insulin, as part of triple therapy, and as a substitute for the free combination of canagliflozin and metformin in these indications.

Clinical data

- The efficacy and safety of canagliflozin have been evaluated in seven phase III studies with the change in the HbA1c level as primary efficacy endpoint.
- In dual therapy with metformin, canagliflozin was superior to placebo at 26 weeks with a difference between the groups of -0.6% in HbA1c at a dose of 100 mg and of -0.8% at a dose of 300 mg in a study that included 1284 patients. A study showed its non-inferiority to glimepiride after 52 weeks of treatment with 26-30% dropouts among the 1452 patients included.
- In triple therapy with metformin and a sulfonylurea, canagliflozin was superior to placebo (difference of -0.7 and -0.9% respectively at the doses of 100 and 300 mg) at 26 weeks in a study that included 469 patients. One study showed the superiority of canagliflozin at a dose of 300 mg only, by comparison with sitagliptin 100 mg with, respectively, 34 and 45% dropouts among the 755 patients included.
- In combination with insulin and metformin, a sub-study showed the superiority of canagliflozin versus placebo (difference of -0.7 and -0.8 at doses of 100 and 300 mg) in a subgroup of 432 patients.
- The data methodology does not allow the efficacy of canagliflozin in monotherapy, in dual therapy with a sulfonylurea or with insulin to be specified.
- The commonest adverse events were hypoglycaemic episodes, urinary and mycotic vulvovaginal infections and pollakiuria/dysuria. Adverse events linked to volume depletion have been found.
- Bioequivalence between the fixed-dose combination canagliflozin/metformin and separate use of each of the active substances has been established for each of the dosages. No phase III study has been performed with the fixed-dose combination. The available efficacy data are from studies that evaluated canagliflozin (INVOKANA).

Benefit of the medicinal product

- The actual benefit* of INVOKANA is:
  - insufficient in monotherapy,
  - substantial in dual therapy in combination with metformin,
  - insufficient in dual therapy in combination with sulfonylureas or insulin,
  - substantial 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 sufficient, given the demonstration of the non-inferiority of canagliflozin by comparison with the active comparators, the absence of any demonstration of its superiority by comparison with sitagliptin at a dosage of 100 mg in particular, and the absence of any long-term safety data, INVOKANA does not provide any clinical added value** (CAV V, none) in the management of type 2 diabetic patients who are inadequately controlled, in oral dual therapy in combination with metformin and in triple therapy in combination with metformin and a sulfonylurea or in combination with metformin and insulin.
- The actual benefit* of VOKANAMET is:
  - substantial in patients insufficiently controlled by metformin alone at the maximum tolerated dose, or combined with a sulfonylurea;
  - moderate in patients whose glycaemic control is insufficient at the maximum dose of metformin combined with insulin;
  - substantial when replacing the free combination of canagliflozin and metformin at the same doses.
- Given the absence of any demonstrated clinical benefit of the fixed-dose combination by comparison with the free combination of metformin and canagliflozin or other oral antidiabetics, VOKANAMET 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 canagliflozin and metformin or indeed in triple therapy in patients insufficiently controlled by the maximum dose of metformin combined with a sulfonylurea or 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".