BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

XIGDUO (dapagliflozin/metformin), antidiabetic

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

Main points

- XIGDUO has Marketing Authorisation in the treatment of type 2 diabetes in adults:
  - in patients not adequately controlled with metformin alone at the maximum tolerated dose.
  - in combination with other blood-glucose lowering medicines, including insulin, in patients not adequately controlled with metformin and those medicines,
  - in patients already being treated with the combination of dapagliflozin and metformin as separate tablets.
- Given the safety profile and modest efficacy of dapagliflozin, the fixed combination has shown no clinical benefit in the management of type 2 diabetes.

Therapeutic use

- The generally recommended use is first of all monotherapy with metformin. If the glycaemic target is not achieved and there is no contraindication to any of the substances, switching to dual therapy combining metformin and a sulfonylurea, then triple therapy combining metformin, a sulfonylurea and a gliptin, or an alpha-glucosidase inhibitor, is recommended.
- The recommended oral antidiabetic treatments in combination with insulin therapy are generally metformin and sulfonylureas.

Role of the medicinal product in the therapeutic strategy

XIGDUO is an additional medicine used in type 2 diabetes that is insufficiently controlled:

- with metformin alone in the maximum tolerated dose.
- with the maximum dose of metformin combined with a sulfonylurea or insulin.

It is preferable to perform a titration with individual tablets to achieve the optimal dose of treatments before using the fixed-dose combination.

Clinical data

- Bioequivalence between the fixed-dose combination and the separate administration of each of the active ingredients has been established. No phase III study has been performed with the fixed-dose combination.
- The available efficacy data are from studies that assessed dapagliflozin (FORXIGA). The efficacy and safety of dapagliflozin have been assessed in six phase III studies with the change in HbA1c as the primary efficacy endpoint.
- In dual therapy in combination with metformin, after 16 weeks of treatment, the reduction in the HbA1c level in favour of the dapagliflozin group compared with the placebo group was - 0.65% versus - 0.30% (difference between the two groups: - 0.35%, 95% CI [-0.52; -0.18]; p<0.0001).
- In triple therapy in combination with metformin and a sulfonylurea, after 24 weeks of treatment, a significantly larger reduction in the HbA1c level in the dapagliflozin 10 mg group compared with the placebo group was seen, with -0.86% versus -0.17% (difference between the two groups: - 0.69%, 95% CI [-0.89; -0.49]; p<0.0001). The impact of this result is limited by the exclusion of data after rescue treatment.
- In triple therapy in combination with metformin and sitagliptin, only exploratory results are available for subgroups of patients formed from a randomised, double-blind, parallel-group study to assess the change in the HbA1c level at 24 weeks on dapagliflozin 10 mg/day in type 2 diabetic patients who are insufficiently controlled on sitagliptin ± metformin.

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The adverse events most commonly observed on dapagliflozin compared with placebo were hypoglycaemia, infections (genital and urinary) and volume depletion, an effect which leads to a precaution for use particularly in patients on antihypertensive treatment or with a cardiovascular disease which more or less corresponds to all diabetic patients.

A long-term safety analysis submitted to the FDA confirms these events and cases of bladder cancer, renal effects and an increase in LDL cholesterol. The recent pharmacovigilance signal on two serious cases of diabetic ketoacidosis raises questions about the safety profile of dapagliflozin and the other two substances in the same therapeutic class.

Special prescribing conditions

- Medicine for initial annual prescription reserved for specialists in endocrinology, diabetes and metabolic disorders or internal medicine. Unrestricted renewal.

Benefit of the medicinal product

- The actual benefit* of XIGDUO is:
  - moderate in patients not adequately controlled by metformin alone at the maximum tolerated dose.
  - moderate in combination with a sulfonylurea in patients whose glycaemic control is inadequate on metformin combined with a sulfonylurea,
  - moderate in combination with insulin in patients whose glycaemic control is inadequate on metformin combined with insulin,
  - moderate in patients already being treated with the combination of dapagliflozin and metformin as separate tablets,
  - insufficient in combination with sitagliptin in patients whose glycaemic control is inadequate on metformin combined with sitagliptin,
  - XIGDUO provides no improvement in clinical added value** (CAV V) in the management of patients with type 2 diabetes.
  - Recommends inclusion on the list of reimbursable products for supply by pharmacies and for hospital use in the indications in which the actual benefit is sufficient.

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* 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”.

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