HAUTE AUTORITÉ DE SANTÉ

DIABETOLOGY
Update
February 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

JARDIANCE (empagliflozin), oral antidiabetic

Insufficient clinical benefit to justify reimbursement for the treatment of patients with type 2 diabetes mellitus due to new safety data.

Main points

- JARDIANCE has an MA for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise, as monotherapy and in addition to other medicinal products for the treatment of diabetes, including insulin.
- Its efficacy has been demonstrated versus sulphonylurea therapy or placebo on the reduction of HbA1c, an interim endpoint, with an effect size judged to be modest.
- JARDIANCE did not result in excess cardiovascular events compared to placebo, without it being able to reach a conclusion with a sufficient level of evidence with respect to any reduction in cardiovascular events and/or total mortality.
- Its safety profile includes a risk of diabetic ketoacidosis, a potential risk of lower limb amputations, and a potential risk of rare but serious cases of Fournier's gangrene. New data are of a nature to call into question the impact of JARDIANCE on morbidity and mortality, particularly in a context in which numerous marketed therapeutic alternatives exist that do not present these signals.

Therapeutic strategy

- The strategy generally recommended is initial monotherapy with metformin. If target blood glucose levels are not obtained and in the absence of contraindications to any of the products, a switch to dual therapy combining metformin and a sulphonylurea, then triple therapy combining, in particular, metformin, a sulphonylurea and gliptin, or an alphaglucosidase inhibitor, is recommended.
- The oral antidiabetic agents recommended in combination with insulin therapy are generally metformin and sulphonylureas.
- **Role of the medicinal product in the therapeutic strategy**
  JARDIANCE no longer has a role in the therapeutic strategy for type 2 diabetes.

Clinical data

- The new data only concern the safety of JARDIANCE. The EMPAREG OUTCOME safety study had demonstrated the non-inferiority, then, as scheduled in the statistical analysis plan, the superiority of combination of empagliflozin, all dosages combined, with standard diabetes therapy compared to placebo combined with standard diabetes therapy, for the 3P-MACE primary composite endpoint of morbidity and mortality. In a post hoc analysis, no difference was demonstrated between the placebo group and the empagliflozin group in terms of lower limb amputation incidence, with a total of 131 concerned patients: 88 patients (1.9%) in the empagliflozin group versus 43 patients (1.8%) for the placebo group: HR = 1.00 95% CI [0.70; 1.44]. In a descriptive safety analysis of grouped data from clinical trials having assessed empagliflozin in T2D patients, the frequency of lower limb amputations was similar between the treatment groups, with 1.1% in all the groups (placebo: 46/4203, empagliflozin 10 mg: 46/4221, empagliflozin 25 mg: 48/4196). No link between empagliflozin and the occurrence of a lower limb amputation was evidenced in this study.
- A recent post-marketing study based on two Swedish and Danish registries concerning a total of 17,213 new users of sodium-glucose co-transporter 2 inhibitors, including 61% of patients receiving dapagliflozin, 38% receiving empagliflozin and 1% receiving canagliflozin versus 17,213 new users of glucagon-like peptide-1 (GLP-

1) revealed a higher rate of amputation (HR = 2.32; 95% CI [1.37-3.91]) and diabetic ketoacidosis (HR = 2.14; 95% CI [1.01-4.52]) in the sodium-glucose co-transporter 2 inhibitor group, with the limitations of an observational study.

- Rare but serious cases of Fournier's gangrene have been identified with gliflozins marketed outside France, including empagliflozin. Cases of potentially life-threatening, rapidly progressing necrotising fasciitis of the perineum and external genitals have been observed, requiring urgent surgery and antibiotic therapy. This risk is included in the summary of product characteristics for the medicinal products concerned.
- The clinical benefit will be re-evaluated for the other 2 gliflozins, i.e. dapagliflozin alone or in combination (FORXIGA and XIGDUO) and canagliflozin alone or in combination (INVOKANA and VOKANAMET).

Special prescription requirements

- Medicinal product subject to initial annual prescription restricted to endocrinology, diabetes and metabolic disease or internal medicine specialists. Unrestricted renewal prescription.

Benefit of the medicinal product

- The actual clinical benefit* of JARDIANCE is insufficient to justify its reimbursement by public funding in its indications.
- Not approved for non-hospital pharmacy reimbursement or for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 27 February 2019 (CT-14177) 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.