HAUTE AUTORITÉ DE SANTÉ

DIABETOLOGY
New medicinal product
March 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

STEGLATRO (ertugliflozin)**, STEGLUJAN**, (ertugliflozin, sitagliptin), oral antidiabetic

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

Main points

- STEGLATRO has an MA for the treatment of type 2 diabetes mellitus as monotherapy in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications, or in addition to other medicinal products for the treatment of diabetes.
- STEGLUJAN has an MA as an adjunct to diet and exercise to improve glycaemic control when metformin and/or a sulphonylurea (SU) and one of the monocomponents of STEGLUJAN do not provide adequate glycaemic control or in patients already being treated with the combination of ertugliflozin and sitagliptin as separate tablets.
- A study only demonstrated the non-inferiority of ertugliflozin 15 mg/d compared to glimepiride, solely for an interim endpoint, the reduction in HbA1C. The non-inferiority of ertugliflozin 5 mg/d compared to glimepiride was not demonstrated.
- Patients exposed to ertugliflozin have a higher risk of genital infections, rare and serious adverse events such as ketoacidosis and lower limb amputations, and uncertainty with respect to a rare but serious potential risk of Fournier's gangrene.

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 products in the therapeutic strategy**
  STEGLATRO and STEGLUJAN have no role in the therapeutic strategy for type 2 diabetes.

Clinical data

- A single non-inferiority study on ertugliflozin versus glimepiride compared the effect size of ertugliflozin as dual therapy with metformin versus a clinically relevant comparator currently recommended in France in combination with metformin, in patients not controlled by metformin alone. However, the non-inferiority of ertugliflozin 5 mg/d compared to glimepiride was not demonstrated. The other studies with ertugliflozin, as monotherapy, as dual therapy with sitagliptin or as triple therapy with sitagliptin and metformin were performed versus placebo. They do not make it possible to assess the effect size and to position ertugliflozin alone or in combination compared to the other diabetes drugs available recommended as monotherapy, dual therapy or triple therapy, depending on the stage in the therapeutic strategy.
- Around 62% of patients included in the 7 clinical studies reported at least one adverse event. The most commonly reported adverse events (AEs) were hypoglycaemia and infections (in particular, urinary, genital and

respiratory). Genital infections were reported in 10.7% of women exposed to ertugliflozin versus 3% of women receiving placebo and in 4.3% of exposed men versus 0.3% of non-exposed men. Osmotic diuresis related to treatment (reported in 4% of patients exposed to ertugliflozin versus 1.6% of patients non-exposed patients) and genital infections represent the two treatment-related adverse events reported more frequently in the group exposed to ertugliflozin than in the non-exposed group. In comparison with glimepiride as dual therapy, ertugliflozin as dual therapy was associated with a lower incidence of hypoglycaemia, which can be explained by the different mechanism of action of these two antidiabetic agents. A total of 21 serious AEs resulting in death were reported: 18 deaths (0.5%) occurring in patients exposed to ertugliflozin and 3 deaths (0.2%) occurring in non-exposed patients. Cardiac causes were the most frequent. A long-term study on the cardiovascular safety of ertugliflozin is ongoing. Three patients treated with ertugliflozin presented ketoacidosis compared to none in the group not treated with ertugliflozin.

- A total of 10 patients underwent a lower limb amputation (usually a toe), including 9 cases in the group exposed to ertugliflozin and 1 case in the group not exposed to ertugliflozin. All amputated patients had at least one risk factor for amputation. This risk had previously been the subject of a European analysis, in February 2017, which concluded that there was an increased risk of lower limb amputation under canagliflozin, without the mechanism responsible being clearly identified, however. Ertugliflozin was not one of the drugs included in the evaluation. A class effect could not be excluded.
- Following the identification of rare but serious cases of Fournier's gangrene (or potentially life-threatening necrotising fasciitis of the perineum and external genitals, requiring urgent surgery and antibiotic therapy) with gliflozins marketed abroad, the European Medicines Agency concluded that there was a class effect and included this risk in the SPCs of the medicinal products concerned, as well as in the risk management plan as an important identified risk.

Special prescription requirements

- Medicinal product subject to initial annual prescription reserved for endocrinology, diabetes and nutrition or internal medicine specialists. Unrestricted repeat prescription.

Benefit of the medicinal product

- The actual clinical benefit* of STEGLATRO and STEGLUJAN is insufficient to justify their reimbursement by public funding in their 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 20 March 2019 (CT-17050, CT-17052) 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.