HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
21 OCTOBER 2020
The legally binding text is the original French opinion version

empagliflozin
JARDIANCE 10 mg, 25 mg film-coated tablets

Reevaluation

Key points

Favourable opinion for reimbursement of JARDIANCE (empagliflozin) only in the treatment of adults with type 2 diabetes mellitus insufficiently controlled by metformin or a sulphonylurea as monotherapy, as an adjunct to diet and exercise, and in combination:
- as dual therapy only with metformin or with a sulphonylurea,
- as triple therapy only with metformin and a sulphonylurea or with metformin and insulin.

Unfavourable opinion for reimbursement of JARDIANCE (empagliflozin) as monotherapy and as dual therapy with insulin.

What therapeutic improvement?

Therapeutic improvement, in the same way as canagliflozin and dapagliflozin, in the treatment of type 2 diabetes mellitus insufficiently controlled by metformin or a sulphonylurea as monotherapy, as an adjunct to diet and exercise, and in combination with other antidiabetic agents.

Role in the care pathway?

The objective of treatment of type 2 diabetes is to prevent the numerous serious and disabling complications, such as microangiopathy (affecting the retina, nerves, heart and kidneys) and sudden complications of macroangiopathy, such as myocardial infarction, stroke, etc. Diabetes promotes the development of heart failure. The Committee also highlights the importance of ensuring patients are well informed and of their compliance with treatment for successful management of the disease. The initial management of type 2 diabetes is based on non-medicinal interventions and, in particular, the implementation of lifestyle and dietary measures. In the event of failure to meet the blood glucose target, medicinal treatment with metformin or, in the event of contraindications, a sulphonylurea is recommended as first-line therapy, in addition to these measures. Drug combinations are envisaged following the failure of monotherapy.

Role of the medicinal product in the care pathway

Following the failure of monotherapy with metformin or a sulphonylurea, a gliflozin, such as canagliflozin, dapagliflozin, empagliflozin, may be chosen as first-line treatment to reinforce and supplement the effect of the drug prescribed as monotherapy, or as second-line dual therapy with metformin or a sulphonylurea. A gliflozin may also be prescribed as third-line drug therapy in the context of triple therapy in combination with metformin and a sulphonylurea, as well as in combination with metformin and insulin.

The choice between the different drug families that can be used as second or third-line treatment (gliflozins, gliptins, alphaglucosidase inhibitors, GLP1 analogues and insulins) will notably be determined on the basis of the safety profile of the medicinal products, the availability of conclusive cardiovascular or renal morbidity and mortality study results and the preferences of patients after they have been given appropriate information.

Empagliflozin, dapagliflozin and canagliflozin present a specific benefit in type 2 diabetics at cardiovascular risk, as primary or secondary prevention, given the results of the EMPA-REG OUTCOME, DECLARE-TIMI 58 and CANVAS studies, having demonstrated the superiority of these drugs compared to placebo in the reduction of MACE for empagliflozin and canagliflozin, and in the reduction of the composite endpoint “cardiovascular death or hospitalisation for heart failure” for dapagliflozin.

Only canagliflozin 100 mg has been the subject of an assessment by the Transparency Committee for the treatment of T2D patients with stage 2 and 3 chronic kidney disease and albuminuria, in combination with standard treatment with ACE inhibitors or angiotensin receptor blockers.

The initiation of gliflozin treatment should be avoided in patients with factors identified as increasing the amputation risk, insofar as an excess amputation risk (mainly of the toe) was identified with canagliflozin versus placebo in the CANVAS programme. Although it was not detected in the clinical studies available, this excess risk cannot be excluded for other drugs in the class.
Potential predisposing factors for amputation are, in particular, a history of amputation, peripheral vascular disease or neuropathy. It is necessary to carefully monitor patients with a higher amputation risk, to inform them and support them to ensure the correct implementation of routine preventive foot care and the maintenance of adequate hydration. Gliflozin treatment must be discontinued in patients who develop events liable to precede an amputation, such as skin ulcers on the lower limbs, an infection or osteomyelitis.

The Committee highlights the fact that JARDIANCE (empagliflozin), like other gliflozins, is also liable to induce:
- ketoacidosis, requiring awareness-raising and patient information. Patients should self-monitor for its development, particularly in the event of non-specific symptoms, such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if

these symptoms occur, regardless of blood glucose level. Patients should be able to test their blood ketone levels themselves if warning signs develop. In patients in whom diabetic ketoacidosis is suspected or diagnosed, treatment should be discontinued immediately.
- genital infections that may precede the development of Fournier's gangrene.
- Fournier's gangrene or necrotising fasciitis. The development of symptoms such as pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise, are warning signs. Uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, treatment with JARDIANCE (empagliflozin) should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

JARDIANCE (empagliflozin) is subject to annual initial prescription restricted to certain specialists (in diabetes, metabolic diseases, endocrinology, internal medicine); with renewal of prescriptions by any prescriber possible.

Given its safety profile, which involves warnings relative to the risk of amputations, ketoacidosis and genital infections, and the very rare but serious and class-specific risk of the development of Fournier's gangrene, the initiation of JARDIANCE (empagliflozin) requires not only a thorough assessment of the patient to make sure he/she does not present an excess risk of development of these events, but also the provision of complete and detailed information to the patient concerning the symptoms associated with each of these events.

The Committee raises the question of whether it might be appropriate to expand annual initial prescription of gliflozins to general practitioners, insofar as type 2 diabetes is a public health issue and its management also depends on these prescribers.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ Diabetes is a chronic disease with potentially serious complications, particularly cardiovascular. The objective of treatment of type 2 diabetes is to prevent its numerous, serious and often disabling complications, that are often insidious, such as microangiopathy (affecting the retina, nerves, heart and kidneys) and sudden complications of macroangiopathy, such as myocardial infarction, stroke, etc. Diabetes promotes the development of heart failure.

◗ These proprietary medicinal products are a preventive treatment for cardiovascular complications of diabetes.

◗ Considering all the clinical data available, the efficacy/adverse effects ratio of JARDIANCE (empagliflozin) is high only:
- as dual therapy with metformin or with a sulphonylurea,
- as triple therapy with metformin and a sulphonylurea or with metformin and insulin.

In the absence of conclusive clinical data, the efficacy/adverse effects ratio of JARDIANCE (empagliflozin) is inadequately established:
- as monotherapy,
- as dual therapy with insulin.

◗ There are numerous therapeutic alternatives

◗ JARDIANCE (empagliflozin) is a first-line medicinal treatment for type 2 diabetes in adults, only as second-line drug therapy, i.e., when the disease is insufficiently controlled by metformin or a sulphonylurea as monotherapy, as an adjunct to diet and exercise, and in combination:
- as dual therapy only with metformin or with a sulphonylurea,
- as triple therapy only with metformin and a sulphonylurea or with metformin and insulin.

JARDIANCE (empagliflozin) has no role in the care pathway as monotherapy or as dual therapy with insulin, in the absence of conclusive clinical data.

◗ Public health impact:
Considering:
- the seriousness of the disease and, in particular, the microvascular and macrovascular complications associated with this disease,
- the high and constantly increasing prevalence of type 2 diabetes,
- the medical need for antidiabetic drugs in type 2 diabetes currently met by medicinal products having demonstrated an efficacy on an intermediate endpoint, HbA1c, and the medical need to have an antidiabetic drug providing evidence of cardiovascular and renal protection,
- efficacy data in terms of reduction of events in the 3P-MACE composite endpoint, and the safety data available, an additional impact of JARDIANCE (empagliflozin) on morbidity and mortality is expected,
- the lack of data on a potential impact on the organisation of care, and the absence of data on a possible impact on quality of life; however, considering the results of the EMPA-REG OUTCOME study on the reduction of occurrence of an event in the 3P-MACE composite endpoint with empagliflozin, an impact of JARDIANCE (empagliflozin) on the organisation of care and quality of life is expected,
- the response provided by JARDIANCE (empagliflozin) to the identified medical need,

JARDIANCE (empagliflozin) is likely to have an additional impact on public health, in the same way as canagliflozin and dapagliflozin.

Considering all these elements, the Committee deems that the clinical benefit of JARDIANCE (empagliflozin) is:

- **substantial in the treatment of adults with type 2 diabetes mellitus insufficiently controlled by metformin or a sulphonylurea as monotherapy, as an adjunct to diet and exercise, and in only in combination:**
  - **as dual therapy only with metformin or with a sulphonylurea,**
  - **as triple therapy only with metformin and a sulphonylurea or with metformin and insulin.**
- **insufficient to justify public funding cover in view of the available alternatives as monotherapy and dual therapy with insulin.**

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the indications of type 2 diabetes mellitus insufficiently controlled by metformin or a sulphonylurea as monotherapy, as an adjunct to diet and exercise, and in only in combination:

- **as dual therapy only with metformin or with a sulphonylurea,**
- **as triple therapy only with metformin and a sulphonylurea or with metformin and insulin,**

and at the MA dosages.

The Committee issues an unfavourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the indications:

- **as monotherapy,**
- **as dual therapy with insulin.**

◗ Recommended reimbursement rate: 65%

Clinical Added Value

Considering:

- **initial data having demonstrated the efficacy of empagliflozin in combination with other treatments, compared to placebo or a sulphonylurea, on reduction of the intermediate laboratory outcome measure, HbA1c, with an effect size deemed to be modest,**
- **demonstration of the superiority of empagliflozin compared to placebo in the EMPA-REG OUTCOME study for a clinically relevant cardiovascular endpoint, i.e., the reduction in events in the 3P-MACE composite endpoint with 3 components (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), in type 2 diabetic patients at high cardiovascular risk,**
- **data that are accumulating for empagliflozin, canagliflozin and dapagliflozin (with the EMPA-REG OUTCOME study, then the CANVAS programme and the DECLARE-TIMI 58 study and, in particular, the meta-analysis by Zheng et al.) demonstrating the clinical benefit of these medicinal products in the prevention of cardiovascular events in type 2 diabetics at cardiovascular risk in primary and secondary prevention, in a context where the traditional drug classes have not demonstrated this,**
- **the medical need to have access to antidiabetic drugs providing evidence of cardiovascular and renal protection, for efficient and optimal management of patients with type 2 diabetes,**

and despite:

- **methodological uncertainties with respect to formal demonstration of the superiority of empagliflozin versus placebo for the 3P-MACE endpoint in the EMPA-REG OUTCOME study in view of the study protocol and the results with the upper limit of the 95% CI very close to 1 (HR= 0.86, 95% CI [0.74-0.99]),**
- **the reduction in absolute cardiovascular risk judged to be low in this study,**

the Committee considers that JARDIANCE (empagliflozin) provides a minor clinical added value (CAV IV), in the same way as canagliflozin and dapagliflozin, in the treatment of type 2 diabetes mellitus insufficiently controlled by metformin or a sulphonylurea as monotherapy, as an adjunct to diet and exercise, and only in combination:

- **as dual therapy only with metformin or with a sulphonylurea,**
- **as triple therapy only with metformin and a sulphonylurea or with metformin and insulin.**