HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
24 MARCH 2021

The legally binding text is the original French opinion version

dapagliflozin
FORXIGA 10 mg film-coated tablets

New indication

Key points

Favourable opinion for reimbursement as salvage therapy only, in addition to optimised standard of care therapy, in adults with chronic heart failure with reduced ejection fraction (LVEF ≤ 40%) who remain symptomatic (NYHA class II to IV) despite this treatment. The Committee considers that optimisation of treatment prior to the prescription of FORXIGA (dapagliflozin) implies having used medicinal products in accordance with the recommended strategy and at the maximum tolerated dose, including ENTRESTO (sacubitril/valsartan) as a potential replacement for an ACE inhibitor or ARB, if their combination is compatible with the patient's clinical profile.

Unfavourable opinion for reimbursement in other populations in the "heart failure" indication, in particular as first-line treatment or in addition to non-optimised standard of care therapy including the valsartan/sacubitril combination (ENTRESTO).

What therapeutic improvement?

Therapeutic improvement in the management of the condition.

Role in the care pathway?

In addition to lifestyle and dietary measures and control of cardiovascular risk factors, the management of adults with symptomatic (NYHA class II to IV) heart failure with reduced ejection fraction is based on optimised standard of care therapy, which includes:
- an angiotensin converting enzyme (ACE) inhibitor, or an angiotensin receptor blocker (ARB) in the event of contraindication or intolerance to ACE inhibitors;
- a beta-blocker, in clinically stable patients only;
- +/- a diuretic (loop or thiazide) in the event of signs and symptoms of congestion.

In patients who remain symptomatic with an LVEF ≤ 35%, despite optimal ACE inhibitor (or ARB) / beta-blocker treatment, it is recommended to add a mineralocorticoid receptor antagonist (MRA) (spironolactone or eplerenone) where possible.

In the event of persistent symptoms and an LVEF ≤ 35% despite optimal ACE inhibitor (or ARB) / beta-blocker / mineralocorticoid receptor antagonist (MRA) treatment, the sacubitril / valsartan (ENTRESTO) fixed-dose combination may be proposed to patients with NYHA class II or III heart failure with an LVEF ≤ 35%, who remain symptomatic despite ACE inhibitor or ARB treatment and require treatment modification (opinion following the reevaluation on 11 January 2017).

Role of the medicinal product in the care pathway

The overall management of chronic heart failure with reduced ejection fraction is based on lifestyle and dietary measures, control of cardiovascular risk factors and a medicinal strategy.

In the medicinal strategy, FORXIGA 10 mg (dapagliflozin) is a salvage therapy, which may be proposed in addition to optimised standard of care therapy, in adults with chronic heart failure with reduced ejection fraction (LVEF ≤ 40%) who remain symptomatic (NYHA class II to IV) despite this treatment.

The Committee considers that optimisation of treatment prior to the prescription of FORXIGA (dapagliflozin) implies having used medicinal products in accordance with the recommended strategy and at the maximum tolerated dose, including ENTRESTO (sacubitril/valsartan) as a potential replacement for an ACE inhibitor or ARB, if their combination is compatible with the patient's clinical profile. It should be noted that in the DAPA-HF study, only 11% of patients were previously treated with ENTRESTO (sacubitril/valsartan).

In other clinical situations of heart failure, in the absence of data, FORXIGA (dapagliflozin) has no role in the care pathway.

As regards safety signals such diabetic ketoacidosis, genital infections, amputations, and Fournier's gangrene observed with gliflozins (including dapagliflozin) in the treatment of type 2 diabetes, in the DAPA-HF study conducted in heart failure patients with or without concomitant type 2 diabetes, the following have been observed:
- 3 confirmed diabetic ketoacidosis events, reported in the dapagliflozin group in diabetic patients;
- 1 genital infection event, reported in the dapagliflozin group in a diabetic patient;
- 13 cases of amputation in the dapagliflozin group and 12 cases in the placebo group, in diabetic or non-diabetic patients;
- no cases of Fournier's gangrene in the dapagliflozin arm versus 1 case in the placebo group reported in a diabetic patient.

The Committee reiterates that it is necessary to conduct a detailed assessment of patients before initiating treatment with FORXIGA (dapagliflozin) in order to ensure that they present no risk factors for the occurrence of such events. It is necessary to provide the patient with comprehensive and precise information relative to the symptoms associated with each of these events, particularly if heart failure is combined with type 2 diabetes.
The precautions relative to these events, particularly in diabetic patients, are highlighted in the reevaluation opinion of 18 November 2020.

◗ Special recommendations

In the DAPA-HF study, conducted in heart failure patients, 43.5% of patients had concomitant type 2 diabetes. The Committee reiterates that the safety profile of FORXIGA (dapagliflozin) requires warnings in patients with type 2 diabetes relative to the risks of amputation, ketoacidosis, genital infection, of the very rare but serious risk and of the very rare but serious and SGLT2 inhibitor class-specific risk of the development of Fournier's gangrene.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Heart failure with reduced ejection fraction is a condition that can progress to more advanced stages and become life-threatening to patients following complications.

◗ The proprietary medicinal product FORXIGA (dapagliflozin) is a medicinal product intended to prevent cardiovascular events in patients with symptomatic heart failure with reduced ejection fraction.

◗ Considering:
- the demonstrated superiority versus placebo on the reduction of cardiovascular events (composite endpoint of cardiovascular death, hospitalisation for heart failure +/- urgent heart failure visit) and on quality of life, only in adult patients with chronic heart failure with reduced ejection fraction (LVEF ≤ 40%) who remain symptomatic (NYHA class II to IV) despite optimised standard of care therapy including the valsartan/sacubitril combination (ENTRESTO);
- the safety profile of dapagliflozin,

the efficacy/adverse effects ratio of dapagliflozin is high in this population.
In other patients[Erreur ! Signet non défini.], the efficacy/adverse effects ratio is not established in the absence of data documenting the efficacy and safety of FORXIGA (dapagliflozin).

◗ There are no therapeutic alternatives in adult patients with chronic heart failure with reduced ejection fraction (LVEF ≤ 40%) who remain symptomatic (NYHA class II to IV) despite optimised standard of care therapy. In other patients, the existing alternatives are described in Chapter 05.

◗ In the medicinal strategy, FORXIGA 10 mg (dapagliflozin) is a salvage therapy, which may be proposed in addition to optimised standard of care therapy, in adults with chronic heart failure with reduced ejection fraction (LVEF ≤ 40%) who remain symptomatic (NYHA class II to IV) despite this treatment. The Committee considers that optimisation of treatment prior to the prescription of FORXIGA (dapagliflozin) implies having used medicinal products in accordance with the recommended strategy and at the maximum tolerated dose, including ENTRESTO (sacubitril/valsartan) as a potential replacement for an ACE inhibitor or ARB, if their combination is compatible with the patient's clinical profile.
In other situations[Erreur ! Signet non défini.], in the absence of clinical data, FORXIGA (dapagliflozin) has no role in the care pathway.

Public health impact

Considering:
- the seriousness of the condition,
- the high prevalence of symptomatic heart failure with reduced ejection fraction,
- the partially met medical need in patients who remain symptomatic despite optimised standard of care therapy,
- the additional response to the identified need given:

- its demonstrated additional impact, in combination with optimised standard of care therapy, on cardiovascular events (composite endpoint of cardiovascular death, hospitalisation for heart failure +/- urgent heart failure visit) and on quality of life, despite the absence of a demonstrated impact on all-cause mortality (exploratory analysis due to interruption of the ranked procedure),
- its potential impact on the organisation of care (marked reduction in hospitalisations for heart failure in the primary composite endpoint),

FORXIGA (dapagliflozin) is likely to have an additional impact on public health.

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

- **substantial as salvage therapy, in addition to optimised standard of care therapy, in adults with chronic heart failure with reduced ejection fraction (LVEF ≤ 40%) who remain symptomatic (NYHA class II to IV) despite this treatment. The Committee considers that optimisation of treatment prior to the prescription of FORXIGA (dapagliflozin) implies having used medicinal products in accordance with the recommended strategy and at the maximum tolerated dose, including ENTRESTO (sacubitril/valsartan) as a potential replacement for an ACE inhibitor or ARB, if their combination is compatible with the patient's clinical profile.**
- **insufficient to justify public funding cover in other populations in the "heart failure" indication, in particular as first-line treatment or in addition to non-optimised standard of care therapy including the valsartan/sacubitril combination (ENTRESTO).**

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 subpopulation of the indication "as salvage therapy, in addition to optimised standard of care therapy, in adults with chronic heart failure with reduced ejection fraction (LVEF ≤ 40%) who remain symptomatic (NYHA class II to IV) despite this treatment" and at the MA dosages.

It issues an unfavourable opinion for inclusion in the other populations of the "heart failure" indication.

- **Recommended reimbursement rate: 65%**

Clinical Added Value

Considering:

- **demonstration in the DAPA-HF study of the superiority of dapagliflozin in combination with optimised standard of care therapy compared to placebo, in a selected population, in terms of:**
  - **reduction in the number of cardiovascular events, a clinically relevant composite endpoint of hospitalisations for heart failure, cardiovascular death and urgent heart failure visits, with an effect size deemed to be relevant (HR=0.74; CI95% [0.65; 0.85]; p<0.0001),**
  - **the improvement in quality of life, which is particularly impaired in this condition, with a clinically relevant difference on the KCCQ score (+2.8 points; WR=1.18; CI95% [1.11; 1.26]; p<0.0001),**
- **the unmet medical need in patients who remain symptomatic despite optimised standard of care therapy,**

but in view of the absence of robust data enabling a conclusion to be reached with respect to all-cause mortality (5th ranked secondary endpoint) due to interruption of the ranked procedure before this endpoint, the Committee considers that the addition of FORXIGA (dapagliflozin) to optimised standard of care therapy provides a minor clinical added value (CAV IV) in the treatment of adults with chronic heart failure with reduced ejection fraction who remain symptomatic despite this treatment.

<u>In other populations in the "heart failure" indication (see insufficient clinical benefit)</u>:
Not applicable.