HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
27 OCTOBER 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 in the treatment of adult patients with chronic kidney disease, in addition to the standard of care therapy:

- with an estimated glomerular filtration rate (eGFR) between 25 and 75 mL/min/1.73m² and a urine albumin to creatinine ratio (UACR) of between 200 and 5,000 mg/g,

- treated for at least 4 weeks with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB or sartan) at the maximum tolerated dose.

Unfavourable opinion for reimbursement in other adult chronic kidney disease populations.

What therapeutic improvement?

Therapeutic improvement in the management of the disease.

Role in the care pathway?

Irrespective of the stage, the treatment objectives in chronic kidney disease (CKD) are to treat the causal disease, slow down kidney disease progression, prevent cardiovascular risks and prevent CKD complications. Control of blood pressure and reduction of albuminuria are essential in the treatment of chronic kidney disease in order to reduce the cardiovascular risk and slow the progression of kidney failure. The choice of treatments and the objectives take into account the existence of hypertension and/or albuminuria, as well as the expected benefits, depending on the context (physiological and chronological age, associated comorbidities, etc.).

Renin-angiotensin system blockers are recommended as first-line treatment. When the objectives (reduction of albuminuria, normalisation of blood pressure) are not attained, the treatment is modified by combining several antihypertensive drug classes: dual therapy, then triple therapy with the aim of normalising blood pressure. In the event of failure, a specialised opinion is recommended.

In the event of diabetic kidney disease, systematic treatment with renin-angiotensin system blockers is initiated in the presence of albuminuria (A/C > 3 mg/mmol) or hypertension (SBP target < 130 mmHg and DBP < 80 mmHg). Since the incidence of hyperkalaemia is increased as a result of renal impairment and acidosis, it needs to be closely monitored in the event of treatment with an angiotensin-converting enzyme (ACE) inhibitor or an ARB.

Canagliflozin (INVOKANA) at a dosage of 100 mg/day demonstrated a benefit in type 2 diabetes with stage 2 or 3 chronic kidney disease and albuminuria for a composite endpoint consisting of “reduction in doubling of serum creatinine, end-stage kidney disease, renal or cardiovascular death” in the phase 3 CREDENCE study. INVOKANA 100 mg (canagliflozin) is recommended as first-line therapy, following the prescription of a stable maximum daily tolerated dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) for at least 4 weeks, in combination with this standard of care therapy. Insofar as canagliflozin lowers blood volume, monitoring of kidney function is important, particularly in the event of concomitant prescription of a diuretic. However, the proprietary medicinal product INVOKANA 100 mg (canagliflozin) is not currently reimbursed or marketed in France.

Role of the medicinal product in the care pathway

Within the reimbursement scope

In view of the efficacy and safety results of the DAPA-CKD study having included adult patients with chronic kidney disease, in addition to standard ACE/ARB treatment administered for at least 4 weeks at the maximum tolerated dose, with an estimated glomerular filtration rate (eGFR) between 25 and 75 mL/min/1.73m² and a urine albumin to creatinine ratio (UACR) of between 200 and 5,000 mg/g, an increase in albuminuria at least 3 months before the first visit, FORXIGA (dapagliflozin) is a first-line treatment only in this population.

FORXIGA (dapagliflozin) treatment is initiated following the prescription of a stable maximum daily tolerated dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) for at least 4 weeks.

The Committee specifies that the progressive nature of chronic kidney disease under ACE or ARB treatment at the maximum tolerated dose is a prerequisite for the initiation of this treatment.

The Committee highlights that 10% of patients included in the DAPA-CKD study had an eGFR between 60 and 75 mL/min/1.73 m^2. The use of dapagliflozin in these patients, particularly in elderly polymedicated patients with slow-progressing kidney failure, should be weighed up against the risks of adding this medicinal product.

In addition, very elderly patients with renal function that is still well preserved (i.e. an eGFR >60 mL/min/1.73 m²), those with a short life expectancy and those whose kidney disease is stable are not suitable for treatment with dapagliflozin.

The Committee recommends that the prescription of FORXIGA (dapagliflozin) be made:

- in consultation with a nephrology specialist in view of the seriousness of the disease and the restricted population recommended for reimbursement,

- by a nephrology specialist for patients with an eGFR between 60 and 75 mL/min/1.73 m² and a urine albumin to creatinine ratio (UACR) of between 200 and 5,000 mg/g.

The absence of a direct comparison with canagliflozin in type 2 diabetics with CKD means that it is not possible to determine the role of dapagliflozin compared to this other medicinal product in this population.

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-CKD study conducted in kidney failure patients with or without concomitant type 2 diabetes, no particular signal was observed among the patients treated with dapagliflozin, with or without type 2 diabetes. One Fournier's gangrene event was reported in the dapagliflozin group. During treatment, 120 (5.6%) patients in the dapagliflozin group versus 84 (3.9%) in the placebo group reported at least one volume deletion-type event.

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 kidney failure is combined with type 2 diabetes. The precautions relative to these events, particularly in diabetic patients, are highlighted in the re-evaluation opinion of 18 November 2020.

Within the scope included in the MA but not retained for reimbursement

In the absence of data, in other clinical situations of chronic kidney disease in adults, FORXIGA (dapagliflozin) has no role in the care pathway.

Special recommendations

In the DAPA-CKD study, conducted in chronic kidney disease patients, the majority of patients (67.5%) 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, and of the very rare but serious and SGLT2 inhibitor class-specific risk of the development of Fournier's gangrene.

The Committee recommends that the prescription of FORXIGA (dapagliflozin) be made:

- in consultation with a nephrology specialist in view of the seriousness of the disease and the restricted population recommended for reimbursement,

- by a nephrology specialist for patients with an eGFR between 60 and 75 mL/min/1.73 m² and a urine albumin to creatinine ratio (UACR) of between 200 and 5,000 mg/g.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Chronic kidney disease is a condition with a natural progression to serious complications, with a significant impact on the patient's quality of life and the healthcare system at the dialysis or transplantation stage, and which can be fatal.

◗ The proprietary medicinal product FORXIGA (dapagliflozin) is a preventive treatment for renal complications.

◗ Considering the results and inclusion criteria of the DAPA-CKD disease, the efficacy/adverse effects ratio is:
- high in adult patients with chronic kidney disease, in addition to standard ACE/ARB therapy administered for at least 4 weeks at the maximum tolerated dose, with an estimated glomerular filtration rate (eGFR) between 25 and 75 mL/min/1.73m² and a urine albumin to creatinine ratio (UACR) of between 200 and 5,000 mg/g,
- inadequately established in the other clinical situations of the MA, in the absence of data supporting the efficacy and safety.

◗ There are medicinal alternatives (see section 05. Clinically relevant comparators).

◗ In view of the efficacy and safety results of the DAPA-CKD study having included adult patients with chronic kidney disease, in addition to standard ACE/ARB treatment administered for at least 4 weeks at the maximum tolerated dose, with an estimated glomerular filtration rate (eGFR) between 25 and 75 mL/min/1.73m² and a urine albumin to creatinine ratio (UACR) of between 200 and 5,000 mg/g, an increase in albuminuria at least 3 months before the first visit, FORXIGA (dapagliflozin) is a first-line treatment only in this population.

Public health impact

Considering:
- the seriousness of the disease, with a natural progression to serious complications, with a significant impact on the patient's quality of life and the healthcare system at the dialysis or transplant stage, and which can be fatal,
- its prevalence and incidence,
- the partially met medical need,
- the additional response provided by FORXIGA (dapagliflozin) to the identified medical need:
    - with a demonstrated additional impact of FORXIGA (dapagliflozin) on morbidity and mortality in terms of reduction of renal events with slowing of kidney damage in the DAPA-CKD study and available safety data,
    - the absence of conclusive data relative to a potential impact on quality of life; nonetheless, given the results provided by the DAPA-CKD study in chronic kidney disease in adults, an additional impact of FORXIGA (dapagliflozin) on quality of life is expected,
- the absence of data relative to a potential impact on the organisation of care; nonetheless, given the results provided by the DAPA-CKD study in chronic kidney disease in adults, an additional impact of FORXIGA (dapagliflozin) on organisation of care is expected,

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 in the treatment of adult patients with chronic kidney disease, in addition to standard therapy:**
  - **with an estimated glomerular filtration rate (eGFR) between 25 and 75 mL/min/1.73m² and a urine albumin to creatinine ratio (UACR) of between 200 and 5,000 mg/g,**
  - **treated for at least 4 weeks with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB or sartan) at the maximum tolerated dose**
- **insufficient to justify public funding cover in view of the available alternatives in other adult chronic kidney disease populations.**

The Committee issues the following opinions:

- 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 treatment of adult patients with chronic kidney disease, in addition to standard of care therapy:

o with an estimated glomerular filtration rate (eGFR) between 25 and 75 mL/min/1.73m² and a urine albumin to creatinine ratio (UACR) of between 200 and 5,000 mg/g,

o treated for at least 4 weeks with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB or sartan) at the maximum tolerated dose
and at the MA dosages.

- unfavourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in other adult chronic kidney disease populations.

- **Recommended reimbursement rate: 65%**

Clinical Added Value

In the treatment of adult patients with chronic kidney disease, in addition to standard therapy, with an estimated glomerular filtration rate (eGFR) between 25 and 75 mL/min/1.73m² and a urine albumin to creatinine ratio (UACR) of between 200 and 5,000 mg/g, treated for at least 4 weeks with an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB or sartan) at the maximum tolerated dose.

Considering:

- **demonstration of the superiority of dapagliflozin compared to placebo, in addition to treatment with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB or sartan), in chronic kidney failure patients with albuminuria, on the composite endpoint including a ≥ 50% decrease in eGFR or end-stage kidney disease or cardiovascular or renal death, a clinically relevant endpoint in the DAPA-CKD study,**
- **with an effect size judged as being high versus placebo for this endpoint (HR=0.61; CI95% [0.51; 0.72]; p<0.0001),**
- **a superiority of dapagliflozin compared to placebo on the three ranked secondary endpoints, including the all-cause mortality endpoint (HR=0.69; CI95% [0.53; 0.88]; p=0.0035),**

- **the safety profile not revealing any particular signal, apart from the known signals characteristic of this drug, including volume depletion, fracture and Fournier's gangrene, making it necessary to take precautions before prescribing dapagliflozin,**
- **the partially met medical need,**
- **but the absence of robust data relative to quality of life, which is particularly impacted in this disease,**

FORXIGA (dapagliflozin) provides a minor clinical added value (CAV III) in the management of adult patients with CKD, in addition to standard of care therapy:
- with an estimated eGFR between 25 and 75 mL/min/1.73m² and a urine albumin to creatinine ratio (UACR) of between 200 and 5,000 mg/g;
- treated for at least 4 weeks with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB or sartan) at the maximum tolerated dose.