OPINION ON MEDICINAL PRODUCTS

fludrocortisone acetate

FLUCORTAC 100 microgramme/mL,

oral solution

First assessment

Adopted by the Transparency Committee on 21 September 2022

SUMMARY

The legally binding text is the original French opinion version

Key points

Approval of reimbursement for:

- replacement therapy in mineralocorticoid deficiency, in combination with a glucocorticoid in primary adrenocortical insufficiency (Addison's disease), and congenital hyperplasia of the suprarenals with salt loss, in all age groups.
- short-term treatment of severe neurogenic orthostatic hypotension requiring pharmacological treatment in all age groups. Fludrocortisone acetate oral solution is only indicated if general and physical measures are not sufficient. The duration of treatment should be as short as possible.

Disapproval of reimbursement in the treatment of severe non-neurogenic orthostatic hypotension.

Therapeutic improvement?

No improvement in the management strategy for primary adrenocortical insufficiency (Addison's disease) and congenital hyperplasia of the suprarenals with salt loss compared to FLUCORTAC (fludrocortisone) 50 µg, scored tablet.

No progress in the management strategy for the treatment of neurogenic orthostatic hypotension compared to the midodrine-based proprietary medicinal products already listed.

Role in therapeutic strategy?

➔ **Primary adrenocortical insufficiency (Addison's disease) and congenital hyperplasia of the suprarenals with salt loss**

Treatment of suspected adrenocortical insufficiency should be started without waiting for the results of hormone assays. Management includes replacement therapy, treatment of the cause, if appropriate, therapeutic education of the patient and close monitoring.

It is based on the combined administration of the deficient hormones:

- hydrocortisone to correct glucocorticoid deficiency;
- fludrocortisone to correct mineralocorticoid deficiency when established (classic form with salt-loss).

Role of the medicinal product

Fludrocortisone is an essential replacement therapy. Fludrocortisone, in combination with a glucocorticoid, is a first-line treatment for primary adrenocortical insufficiency in the event of mineralocorticoid deficiency (Addison's disease) and congenital hyperplasia of the suprarenals with salt loss in all age groups.

Fludrocortisone is an aldosterone analogue. It must be systematically combined with hydrocortisone for the treatment of adrenocortical insufficiency, as its glucocorticoid activity is too weak for it to be used as a monotherapy at the usual dosages. In primary adrenocortical insufficiency, fludrocortisone is the essential replacement therapy.

FLUCORTAC (fludrocortisone) 100 mcg/mL, oral solution, is an additional therapeutic option for replacement therapy in mineralocorticoid deficiency, primary adrenocortical insufficiency (Addison's disease) and congenital hyperplasia of the suprarenals with salt loss.

The Committee underlines the practical value of this new formulation of FLUCORTAC (fludrocortisone) oral solution for use in newborns and young children, and in patients with swallowing disorders.

➔ **Orthostatic hypotension**

According to the recommendations, as soon as the diagnosis is made, dietary and hygiene measures must be proposed: eradication of aggravating factors (antihypertensive treatment, anaemia, dehydration), education of the patient by teaching him/her to get up progressively, to avoid overly abundant and rich meals, to avoid excessively hot environments (leading to peripheral vasodilatation), and to increase his/her daily salt intake (if possible). If symptoms persist, non-medicinal measures such as compression stockings or tights are suggested. If the hypotension is drug-induced, adjusting the dosage, or avoiding or discontinuing the treatment are recommended.

In the event of failure, midodrine and fludrocortisone are the two pharmacological treatments that can be considered. It should be noted that according to the ESC recommendations, there is better evidence of the efficacy of midodrine for the treatment of orthostatic hypotension than fludrocortisone. In addition, the French national diagnosis and treatment protocol (PNDS) (Familial Amyloid Neuropathy – April 2017), recommends the use of fludrocortisone after the failure of midodrine.

To date, there are no specific recommendations for the management of severe orthostatic hypotension.

Role of the medicinal product

Despite the low level of evidence presented by efficacy data, FLUCORTAC (fludrocortisone) oral solution is amongst the recommended first-line treatments for the short-term management of severe neurogenic orthostatic hypotension requiring pharmacological treatment in all age groups. Fludrocortisone acetate oral solution is only indicated if general and physical measures are not sufficient.

The Committee underlines the practical benefit of this new formulation of FLUCORTAC (fludrocortisone) oral solution for use in patients with swallowing disorders and in paediatrics.

Committee's conclusions

Clinical Benefit

Primary adrenocortical insufficiency (Addison's disease) and congenital hyperplasia of the suprarenals with salt loss

- ➔ Adrenocortical insufficiency results from a deficient production of adrenal hormones (glucocorticoid and/or mineralocorticoid). If left untreated, it leads to a marked deterioration in quality of life and is life-threatening, especially in the congenital form.
- ➔ FLUCORTAC (fludrocortisone) 100 µg/mL, oral solution is a symptomatic proprietary medicinal product and an essential replacement therapy for primary adrenocortical insufficiency.
- ➔ The efficacy/adverse effect ratio is significant.
- ➔ Alternative medications are available.
- ➔ First-line treatment for mineralocorticoid deficiency in the management of primary adrenocortical insufficiency (Addison's disease) and congenital hyperplasia of the suprarenals with salt loss.

Public health benefit

Considering:

- the marked deterioration in quality of life and disability associated with severe orthostatic hypotension,
- the difficulty of estimating its prevalence and the small proportion of patients requiring an oral solution (children and people with swallowing disorders),
- the fact that FLUCORTAC (fludrocortisone) 100 µg/mL, oral solution, is the only formulation of fludrocortisone in an oral solution formulation that meets the medical need for pharmaceutical dose forms adapted to administration in children (particularly newborns) and adults with swallowing disorders,
- the potentially positive impact of FLUCORTAC (fludrocortisone) oral solution on the delivery of care (ease of administration), as reported by patient associations,
- and despite the lack of robust evidence of an impact on morbidity-mortality and quality of life, but considering the established use of fludrocortisone,

FLUCORTAC (fludrocortisone) 100 µg/mL, oral solution is likely to have an impact on public health.

Taking into account all these elements, the Committee deems that the actual clinical benefit of FLUCORTAC (fludrocortisone) 100 µg/mL, oral solution, is substantial as a replacement therapy in the event of mineralocorticoid deficiency, in combination with a glucocorticoid, in primary adrenocortical insufficiency (Addison's disease) and in congenital hyperplasia of the suprarenals with salt loss, in all age categories.

The Committee approves inclusion in the list of proprietary medicinal products qualifying for reimbursement under social security and in the list of proprietary medicinal products approved for community use as a replacement therapy in the event of mineralocorticoid deficiency in the indication and at the dosages of the marketing authorisation.

Recommended reimbursement rate: 65%

Orthostatic hypotension

➔ Severe orthostatic hypotension is a potentially serious and disabling condition because of the risk of falls, which can lead to complications and impaired quality of life.

➔ This proprietary medicinal product falls within the scope of symptomatic treatment.

➔ The efficacy/adverse effect ratio is poorly defined due to the lack of robust efficacy data for FLUCORTAC (fludrocortisone).

➔ Therapeutic alternatives are available, particularly midodrine.

FLUCORTAC (fludrocortisone) is one of the recommended first-line therapies for the management of neurogenic orthostatic hypotension when non-medicinal measures have failed.

➔ Public health benefit

Considering:

- the marked deterioration in quality of life and disability associated with severe orthostatic hypotension,
- the difficulty of estimating its prevalence and the small proportion of patients requiring an oral solution (children and people with swallowing disorders),
- the fact that FLUCORTAC (fludrocortisone) 100 µg/mL, oral solution, is the only formulation of fludrocortisone in an oral solution formulation that meets the medical need for pharmaceutical dose forms adapted to administration in adults with swallowing disorders and children,
- and despite the lack of robust evidence of an impact on morbidity-mortality and quality of life, but considering the established use of fludrocortisone,

FLUCORTAC (fludrocortisone) 100 µg/mL, oral solution is likely to have an impact on public health.

Considering all of these elements, the Committee deems that the actual clinical benefit of FLUCORTAC (fludrocortisone) 100 µg/mL, oral solution, is:

- **low only for the short-term treatment of severe neurogenic orthostatic hypotension requiring pharmacological treatment in all age groups;**
- **insufficient, in patients with non-neurogenic orthostatic hypotension, to justify public funding in view of the available alternatives.**

The Committee approves inclusion in the list of proprietary medicinal products qualifying for reimbursement under social security and in the list of proprietary medicinal products approved for community use in the short-term treatment of severe neurogenic orthostatic hypotension requiring pharmacological treatment, in addition to non-medicinal measures, and when general and physical measures are not sufficient.

Recommended reimbursement rate: 15%

Clinical Added Value

Primary adrenocortical insufficiency (Addison's disease) and congenital hyperplasia of the suprarenals with salt loss

Considering:

- **the well-established use of fludrocortisone in the treatment of primary adrenocortical insufficiency in the event of mineralocorticoid deficiency;**
- **the practical value of this formulation, particularly in newborns, without clinical data to support claims of a quality-of-life or compliance benefit,**

the Transparency Committee deems that FLUCORTAC (fludrocortisone) 100 µg/mL, oral solution, provides no clinical added value (CAV V) compared to the fludrocortisone-based speciality already listed, FLUCORTAC (fludrocortisone) 50 µg, scored tablet.

Orthostatic hypotension

Considering:

- **the poor quality of the evidence suggesting a modest increase in blood pressure when moving to a standing position (old, mainly non-comparative studies with a small number of patients),**
- **the lack of comparative efficacy and safety data compared to midodrine,**
- **the medical need for alternatives and the well-established use of fludrocortisone for the treatment of neurogenic orthostatic hypotension,**
- **the lack of demonstration of the practical value of this formulation in terms of quality of life or compliance,**

the Transparency Committee deems that FLUCORTAC (fludrocortisone) 100 µg/mL, oral solution, provides no clinical added value (CAV V) for the management of neurogenic orthostatic hypotension.