HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
5 MAY 2021

The legally binding text is the original French opinion version

osilodrostat
ISTURISA 1 mg film-coated tablets
ISTURISA 5 mg film-coated tablets
ISTURISA 10 mg film-coated tablets

First assessment

Key points

Favourable opinion for reimbursement in the treatment of endogenous Cushing's syndrome in adults.

What therapeutic improvement?

Therapeutic improvement in the same way as the other medicinal products containing ketoconazole and metyrapone available for treatment of the condition.

Role in the care pathway?

Treatments should be discussed in the context of a multidisciplinary care approach, based on the diagnosis, the impact of the disease and comorbidities.

The first-line treatment in Cushing's syndrome consists of surgical excision if the tumour is clearly defined.

But if surgery fails, non-medicinal treatments may be envisaged, such as: revision surgery, pituitary gland radiotherapy, bilateral adrenalectomy. In Cushing's syndrome, medicinal treatments containing ketoconazole or metyrapone are a postoperative option in the event of persistent hypercortisolism, in the event of recurrences or a high surgical risk, or if surgery is impossible.

The medicinal treatments currently used in endogenous Cushing's syndrome are aimed at controlling biochemical and clinical hypercortisolism. They can be categorised based on their target, mainly pituitary or adrenal, bearing in mind that those acting on the pituitary gland are reserved for use in Cushing's disease, whereas medicinal products acting on the adrenal glands may be used in all the indications. According to the experts, their combination may be useful in the event of severe hypercortisolism.

Medicinal products with a pituitary action are:

- Pasireotide (SIGNIFOR), which has an MA only in the treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed.
- Cabergoline, a dopaminergic analogue, which appears to reduce ACTH (adrenocorticotrophin) secretion, but which is used off-label, in the absence of a controlled study (the available studies are conducted with small sample sizes and over the short term).

The following medicinal products with an adrenal action (blocking of the adrenal enzymes involved in cortisol secretion) are indicated in Cushing's syndrome. The Transparency Committee considered that they were alternatives in the care pathway in patients for whom surgery is not an option or for whom surgery has failed, or in severe forms of hypercortisolism. Their prescription requires the opinion of a multidisciplinary team specialised in the management of endogenous Cushing's syndrome.

- Metyrapone, an enzyme inhibitor specific to 11β hydroxylase (enzyme essential for the synthesis of cortisol in the adrenal gland) has a short action onset. Used over the long term, this proprietary medicinal product can cause signs of hyperandrogenism in women.
- Mitotane (LYSODREN) is indicated in the symptomatic treatment of advanced adrenal cortical carcinoma (ACC). Its associated adverse effects (neurological effects, hypercholesterolemia and hypouricemia, in particular) limit its use.
- Ketoconazole, a steroidogenesis inhibitor, has a short action onset. The prescription of ketoconazole requires regular and frequent monitoring of liver enzyme levels due to a hepatotoxic risk. Despite its hepatotoxic risk and according to expert opinion, ketoconazole appears to be better tolerated than metyrapone and mitotane, in particular. In Cushing's disease, a risk of treatment resistance may be expected in the medium term, due to the reduction in cortisol, leading to a reactive increase in ACTH (adrenocorticotrophin).

Role of ISTURISA (osilodrostat) in the care pathway

Considering:
- demonstration of the superiority of osilodrostat versus placebo:
  * in patients predominantly with Cushing's disease in whom surgery has failed,
  * on a biological endpoint (mUFC) and in the short term, but in a context of a slow-progressing and polymorphous disease, making this an acceptable efficacy endpoint,
- its safety profile, including long-term uncertainties and the identified risk in the Risk Management Plan concerning QT prolongation,

ISTURISA (osilodrostat) is an additional treatment option in endogenous Cushing's syndrome, in the same way as medicinal products containing ketoconazole or metyrapone, in patients for whom surgery is not an option or for whom surgery has failed, or in severe forms of hypercortisolism.

There is no comparative data versus the other medicinal products available in the treatment of Cushing's syndrome, meaning that the drug cannot be positioned compared to these.

The choice between these medicinal products should be made in view of the level of evidence of the data available, the safety profile, and the patient's characteristics and preferences.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Endogenous Cushing's syndrome is a rare disease, related to multiple aetiologies, of pituitary, adrenal or ectopic origin. Pituitary adenoma, or Cushing's disease, is the most common cause. The complications of Cushing's syndrome, related to hypersecretion of cortisol, notably include an increase in cardiovascular (venous thrombosis and pulmonary embolism, hypertension), metabolic (diabetes, dyslipidemia, etc.), infectious, psychiatric and osteoporosis risks. It is a serious disease that can be life-threatening.

◗ The proprietary medicinal product ISTURISA (osilodrostat) is a symptomatic medicinal product to treat hypercortisolism.

◗ The efficacy/adverse effects ratio is high.

◗ There are therapeutic alternatives (see chapter **Erreur ! Signet non défini.**. Clinically relevant comparators).

◗ It is an additional treatment option in endogenous Cushing's syndrome, in the same way as medicinal products containing ketoconazole or metyrapone, in patients for whom surgery is not an option or for whom surgery has failed, or in severe forms of hypercortisolism.

Public health impact

Considering:

- the seriousness of endogenous Cushing's syndrome and its rarity, with a prevalence of between 5.9 and 6.5/100,000[Erreur ! Signet non défini.],
- the partially met medical need,
- the lack of additional response to the identified need:
    - with no demonstrated impact on morbidity and mortality and on quality of life, with only demonstrative data on a biological endpoint (mUFC) in the short term, and with no demonstrative data on quality of life,
    - the absence of an additional impact on the organisation of care,

ISTURISA (osilodrostat) is not liable to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of ISTURISA (osilodrostat) is substantial in the MA indication.

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 marketing authorisation indication and dosages.

◗ **Recommended reimbursement rate: 65%**

Clinical Added Value

Considering:

- demonstration of the superiority of osilodrostat versus placebo, with 77% responders for the normalisation of urinary free cortisol in the osilodrostat group and 8% in the placebo group, i.e., an OR = 43.4 (CI95%= [7.06; 343.19]; p>0.001) at 12 weeks, in a phase 3, multicentre, double-blind study in patients with Cushing's disease, for the majority of whom surgery has failed,
- a demonstration obtained only on a biological endpoint and in the short term, in a context of a slow-progressing and polymorphous disease, making this an acceptable efficacy endpoint,
- the absence of data versus current clinically relevant comparators, in a context in which this comparison was not possible,

and despite:

- the absence of data on a clinically relevant endpoint,
- the absence of robust data on quality of life, in a disease that has a significant impact on this, which is regrettable,
- the limited follow-up in terms of safety, and the important identified risk in the RMP (risk management plan) on QT prolongation,
- the medical need partially met by the available alternatives,

the Committee considers that ISTURISA **(osilodrostat) provides a minor clinical added value (CAV IV), in the same way as medicinal products containing ketoconazole and metyrapone, in the current care pathway.**