BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

METYRAPONE HRA PHARMA (metyrapone), treatment of endogenous Cushing’s syndrome and test for pituitary function

Minor improvement in the treatment of endogenous Cushing’s syndrome. No clinical benefit demonstrated as a dynamic test exploring the function of the hypothalamic-pituitary-adrenal axis.

Main points

- METYRAPONE HRA PHARMA has Marketing Authorisation in the treatment of patients with endogenous Cushing’s syndrome, the diagnosis of ACTH deficiency, and the differential diagnosis of ACTH-dependent Cushing’s syndrome.
- The data from clinical studies offer low levels of proof in the treatment of Cushing’s syndrome without any convincing demonstration of benefit in terms of diagnostic performance.
- Metyrapone’s delayed action is short, with a plasma peak reached in 1 hour.
- It forms part of the arsenal of protocols exploring the function of the hypothalamic-pituitary-adrenal axis.

Therapeutic use

- The first-line treatment for Cushing’s syndrome generally consists in the surgical excision of the tumour once it has been properly identified and if it is surgical. In the event of failure or should surgical treatment prove impossible, or in the event of a relapse following complete remission, several second-line treatments may be considered, though there is no consensus on their respective merits:
  - a fresh surgical intervention or pituitary radiotherapy in Cushing’s disease,
  - second-line bilateral adrenalectomy in Cushing’s disease as well as in paraneoplastic syndromes,
  - medicinal treatment in all indications of Cushing’s syndrome.
- Medicinal treatments may be used in:
  - Cushing's disease: in severe forms of hypercorticism, preoperatively in the case of persistent hypercorticism, in cases of relapse, or if surgery is impossible or subject to high operative risk;
  - ACTH-dependent syndromes of ectopic origin: in severe forms of hypercorticism, metastatic or unresectable cancers or high operative risk;
  - adrenal cancer or hyperplasia: in severe forms of hypercorticism, if surgery is impossible or subject to high operative risk, as an adjuvant treatment for a corticoadrenaloma.
- The tests used for the diagnosis of ACTH deficiency are the SYNACTHEN test and the insulin hypoglycaemia test. For the differential diagnosis of Cushing’s syndrome, the dexamethasone test, the CRH test, and inferior petrosal sinus sampling are used.
- Role of the medicinal product in the therapeutic strategy
  Before prescribing metyrapone it is necessary to have the opinion of a multidisciplinary team expert in the management of endogenous Cushing’s syndrome. Despite the methodological limitations of studies that have assessed its efficacy, and taking account of its speed of action and tolerability profile, METYRAPONE HRA PHARMA can be used in endogenous Cushing’s syndrome, as one of the suitable alternatives, in the following situations: when surgery has been ruled out, after failure of surgery, or in severe forms of hypercorticism. Like the insulin hypoglycaemia test (reference test), the metyrapone test does make it possible to assess the response of the corticotropic axis and forms part of the arsenal of protocols for the functional exploration of the hypothalamic-pituitary-adrenal axis.
Clinical data

- The data on the use of metyrapone are based on a review of the literature. In the treatment of Cushing’s syndrome, the available data, which offer a low level of proof (non-comparative retrospective studies with small numbers of included patients, combined with radiotherapy), do show metyrapone to be effective.
- Following the metyrapone test, urinary concentrations of 17-OHCS and 17-CS and plasma concentrations of 11-DOCS increase in patients with Cushing’s disease, adrenal hyperplasia and nodular adrenal hyperplasia. Conversely, patients with adrenal cancer and ectopic ACTH secretion syndrome show no such increase.
- Adverse events include: nausea, vomiting, dizziness, skin rash, sedation, headache, aggravation of hypertension, oedema, hypokalaemia. Used long-term, metyrapone can produce signs of hyperandrogenism in women.

Special prescribing conditions

- Medicine for hospital prescription only.

Benefit of the medicinal product

- The actual benefit* of METYRAPONE HRA PHARMA is substantial.
- In light of its efficacy, speed of action and tolerability profile, METYRAPONE HRA PHARMA, like KETOCONAZOLE HRA, provides minor clinical added value (CAV IV) in the treatment strategy for endogenous Cushing’s syndrome. METYRAPONE HRA PHARMA does not provide clinical added value (CAV V) as a dynamic test exploring the function of the hypothalamic-pituitary-adrenal axis.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

* The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means “no clinical added value”.

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