HAUTE AUTORITÉ DE SANTÉ

ENDOCRINOLOGY
New medicinal product
May 2015

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

KETOCONAZOLE HRA (ketoconazole), imidazole

Minor improvement in the management of endogenous Cushing's syndrome in patients aged over 12 years

Main points

- KETOCONAZOLE HRA has Marketing Authorisation in the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years.
- In retrospective studies with a number of methodological limitations, its efficacy was demonstrated by a reduction in 24-hour urinary free cortisol and in clinical symptoms and comorbidities, in particular arterial hypertension and diabetes.
- Because of the known hepatic toxicity of ketoconazole, regular monitoring of liver function and tailoring of the dosage are essential.

Therapeutic use

- Treatments need to be discussed as part of an interdisciplinary management strategy based on the diagnosis, impact of the condition and comorbidities.
- In the case of well-defined tumours, the first-line treatment is generally surgical excision. If surgical treatment is unsuccessful or not possible or in the event of recurrence after complete remission, a number of second-line treatments can be considered, with no consensus on their role:
  - renewed surgery or radiotherapy of the pituitary in Cushing's disease,
  - bilateral adrenalectomy as second-line treatment in Cushing's disease and paraneoplastic syndromes,
  - drug therapy in all indications of Cushing's syndrome.
- Drug therapies may be used in:
  - Cushing's disease: in patients with severe forms of hyperadrenocorticism, postoperatively in patients with persistent hyperadrenocorticism, in the event of recurrence or if surgery is not possible or too risky;
  - ACTH-dependent ectopic syndromes: in severe forms of hyperadrenocorticism, in metastatic or unresectable tumours or if surgery is too risky;
  - tumours or adrenal hyperplasia: in severe forms of hyperadrenocorticism, if surgery is not possible or too risky or as adjuvant treatment of adrenocortical carcinoma.

Role of the medicinal product in the therapeutic strategy

KETOCONAZOLE HRA can be used in endogenous Cushing's syndrome as one of the suitable treatment options in the following situations: when surgery is not possible or has been unsuccessful or in severe forms of hyperadrenocorticism.

Its prescription must be approved by an interdisciplinary team with expertise in the management of endogenous Cushing's syndrome and necessitates regular and frequent monitoring of liver enzymes.

Clinical data

- In three main recent retrospective studies that included a total of approximately 300 patients, the efficacy of ketoconazole was described on the basis of two criteria: biochemical (normalisation or reduction of 24-hour urinary free cortisol) and clinical (improvement in clinical symptoms and comorbidities, in particular arterial hypertension and diabetes).
- These studies observed a biochemical improvement in 43 to 50% of patients, and in up to 85% in one of the studies. The improvement in the clinical signs was not rigorously correlated with the improvement in biochemical parameters, with the disease clinically monitored in 32% of patients in one study and in approximately 50% of patients in the other two studies.
- Data on ketoconazole dose and duration of treatment are difficult to exploit, as values vary considerably from one study to the next. Given the retrospective and non-comparative nature of these studies and the lack of statistical adjustment and inclusion of patients with varying profiles, the results are essentially exploratory.
- The most frequent adverse events were liver enzyme elevations (between 5 and 16%), which were especially common during the first month of treatment, skin disorders (approx. 3%), adrenal insufficiency (3 to 19%) and poor gastrointestinal tolerability.

Benefit of the medicinal product

- The actual benefit* of KETOCONAZOLE HRA is substantial.
- Taking into account its efficacy, rapidity of action and safety profile, KETOCONAZOLE HRA provides minor clinical added value** (CAV IV) in the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 20 May 2015 (CT-14104) and is available at **www.has-sante.fr**

[i] * 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".