HAUTE AUTORITÉ DE SANTÉ

GYNAECOLOGY
Update
February 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

ESMYA (ulipristal acetate), progesterone receptor modulator

Insufficient clinical benefit to justify reimbursement for the treatment of uterine fibroids

Main points

- ESMYA has an MA for one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age and for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery.
- ESMYA no longer has a role in the therapeutic strategy in its two indications on the basis of new safety data.

Therapeutic strategy

- No currently validated medical treatment for myoma-related symptoms is capable of making myomas disappear. Therefore in the event of asymptomatic fibroids, there is no point envisaging treatment. In the presence of symptomatic fibroids (pain or bleeding), the objective of medical therapy is solely to treat the symptoms associated with the myomas. The first-line treatment for submucosal fibroids is surgical management.
- Progestagens: the prescription of progestagens is not a treatment for myomas; it may be proposed to treat myoma-related menometrorrhagia in the short to medium term. Intrauterine progestagen treatment (IUD releasing levonorgestrel) for fibroid-related menometrorrhagia is validated, except in submucosal fibroids and those deforming the uterine cavity.
- Antifibrinolytic agents: uterine myoma-related menorrhagia is maintained by local fibrinolysis. Tranexamic acid is effective in the treatment of myoma-related menorrhagia.
- GnRH analogues: these may only be used occasionally, and in a pre-operative context, due to their adverse reactions.

- **Role of the medicinal product in the therapeutic strategy**

  Considering:
  - the rare but serious hepatic adverse reactions that may occur from the first 3-month sequence of treatment with ESMYA, and:
  - in its pre-operative indication, the existence of a clinically relevant comparator, leuprorelin, versus which ESMYA has not demonstrated its superiority in terms of efficacy (non-inferiority study) and for which no serious safety problems of the same magnitude as those reported with ESMYA have been reported,
  - in sequential treatment, the absence of comparative efficacy data versus medicinal products indicated in the management of functional bleeding and/or fibroid-related menorrhagia (in particular progestagens), for which no serious safety problems of the same magnitude as those reported with ESMYA have been reported,
  - the absence of efficacy or safety data at the MA dose (5 mg/d) beyond four 3-month treatment sequences and, in particular, long-term uncertainties relative to endometrial safety, due to histological changes observed in clinical studies.

  There is a potential loss of opportunity for patients if they receive ESMYA instead of the available alternatives. Consequently, ESMYA no longer has a role, as pre-operative treatment or sequential treatment, in the therapeutic strategy for moderate to severe symptoms of uterine fibroids.

Clinical data

- New efficacy data:
  - A randomised, double-blind, placebo-controlled trial in 3 parallel groups (around 50 patients/group) (VENUS I) studied the efficacy of treatment of symptomatic uterine fibroids with ulipristal acetate at the doses of 5 mg/d or 10 mg/d for 12 weeks. Only the efficacy results obtained with the daily dose of 5 mg and under placebo are presented, the daily dose of 10 mg being off-label. A significant difference versus placebo, in favour of ulipristal 5 mg/d, was demonstrated for the two primary combined endpoints: proportion of patients with amenorrhea for the past 35 consecutive days of treatment and time to absence of bleeding under treatment.
  - The pharmaceutical company also submitted 4 published studies concerning the effect of pre-operative treatment with ESMYA on the result of hysteroscopic or laparoscopic myomectomies. The methodological biases of these studies mean that it is not possible to reach a conclusion concerning the efficacy of ESMYA on the outcome measures of these studies: complete resection percentage, mean duration of procedure, surgical difficulty score, intraoperative blood loss.
- New safety data
  - PRAC conclusions:

The PRAC analysed pharmacovigilance reports collected from the time of marketing of ESMYA up until 28 February 2018, as well as follow-up data concerning 6 serious cases received up until April 2018. In total, 105 cases of “liver injury” were identified, including 71 non-serious cases and 34 serious cases. For 8 of these serious cases, a possible role of ESMYA was identified. Among these, 4 cases of acute liver failure required liver transplantation. Although the observation of missing data for all the post-marketing cases reported hampers the causality assessment, the information available is sufficient to conclude that there is at least a reasonable possibility that ESMYA may contribute to liver injury in rare cases.

  - Venus I study

Adverse events were reported by 28.6% of patients in the placebo group, 43.4% in the 5 mg group and 54.2% in the 10 mg group. The most common adverse events were observed in the treated groups: hot flushes, elevated CPK, exacerbation of hypertension. Endometrial changes associated with progesterone receptor modulators concerned 13.6% of patients in the placebo group, 26.2% of patients in the 5 mg group and 29.7% of patients in the 10 mg group at the end of treatment. At the end of the 12-week follow-up period, they concerned 7.1%, 19.0% and 12.1% of patients respectively.

  - PEARL study extension II:

This trial studied the efficacy and safety of 10 mg/d (off-label) of ulipristal administered for four 12-week sequences in 64 patients having already received 4 sequences of treatment during previous studies. The most common adverse events during the treatment sequences were hot flushes (0 to 3.6% of patients depending on the sequence) and headaches (3.1 to 4.8%). An ectopic kidney was diagnosed in a child exposed to the treatment in utero up to 7 weeks of gestation.

On inclusion in the study, the median endometrial thickness, measured in 34 women, was 8 mm (3 to 17 mm); 1 woman had an endometrial thickness >16 mm. After cycles 6 and 8 as well as 3 months after the last dose of ulipristal, the median endometrial thickness was 7 mm; the maximum thickness was 16 mm after cycle 6 and after the end of treatment; after cycle 8, one woman had an endometrial thickness >16 mm (23 mm). After the end of cycle 8, two benign polyps were diagnosed on endometrial biopsy, absent on the biopsy performed 3 months later.

Special prescription requirements

- Prescription reserved for gynaecology or obstetrics specialists.

Benefit of the medicinal product

- The actual clinical benefit* of ESMYA is insufficient to justify its reimbursement by public funding in its two indications.
- Not approved for non-hospital pharmacy reimbursement or for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 27 February 2019 (CT-17283) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a 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 ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.