HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
18 MAY 2022

The legally binding text is the original French opinion version

relugolix / estradiol / norethisterone acetate
RYEQO 40 mg / 1 mg / 0.5 mg film-coated tablets

First assessment

Key points

Favourable opinion for reimbursement in the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

What therapeutic improvement?

No clinical added value in the therapeutic strategy for the treatment of moderate to severe symptoms of uterine fibroids.

Role in the care pathway?

In the event of asymptomatic fibroids, there is no point envisaging medical treatment. With the exception of symptomatic submucosal fibroids, in which the first-line treatment is surgery, the first-line treatment of symptomatic fibroids with pain or bleeding, is symptomatic. No medical treatment for fibroid-related symptoms is effective in terms of making fibroids disappear.

The prescription of a progestogen treatment is aimed at reducing menometrorrhagia by reducing fibroid-related endometrial hyperplasia. Three progestogen-containing medicinal products are indicated in the treatment of fibroid-related functional bleeding and menorrhagia: COLPRONE (medrogestone), LUTENYL (nomegestrol), LUTERAN (chlormadinone).

A risk of meningioma has been confirmed with chlormadinone acetate (LUTERAN) and nomegestrol (LUTENYL), which increases on the basis of the dose, the treatment duration and the patient's age. When these medicinal products are used for less than a year, the risk of meningioma is very low. Beyond this period, the risk is significantly increased. Consequently, beyond a period of one year, their prescription must be reassessed annually, with the implementation of brain MRI monitoring. Their risk/benefit ratio is considered to be favourable in women of reproductive age when the therapeutic alternatives have failed or are contraindicated in fibroid-related functional bleeding and menorrhagia before surgery.

A levonorgestrel-releasing intrauterine system (MIRENA or DONASERT) is indicated in functional menorrhagia, after investigating for and ruling out detectable organic causes. A levonorgestrel-releasing intrauterine system is contraindicated in the event of congenital or acquired abnormalities of the uterus, including fibroids if they distort the uterine cavity. Due to the increased risks of bleeding complications and expulsion, submucosal fibroids are a relative contraindication to intrauterine devices.

The proprietary medicinal products EXACYL and SPOTOF, containing tranexamic acid, are indicated in haemorrhage caused by local fibrinolysis, as is the case in menorrhagia and metrorrhagia secondary to traumatic or infectious or degenerative lesions of the uterus.

Mefenamic acid (PONSTYL) is indicated in functional menorrhagia that remains unexplained following systematic aetiological analysis and dysmenorrhoea following aetiological investigation.

According to the French national college of gynaecologists-obstetricians (CNGOF), nonsteroidal anti-inflammatories (NSAIDs) can lead to a reduction in menorrhagia, but with a lower efficacy than tranexamic acid or the levonorgestrel-releasing intrauterine system. They are effective in the event of pain related to aseptic necrobiosis of a fibroid. The prescription of NSAID treatment may be proposed to treat the symptoms of fibroids.

Three proprietary medicinal products containing GnRH agonists, GONAPEPTYL (triptorelin), DECAPEPTYL (triptorelin) and ENANTONE (leuprorelin), have an MA in the preoperative treatment of uterine fibroids to reduce their size and/or correct anaemia. They are reserved for short-term use (3 to 6 months depending on the medicinal product) in severe cases before elective surgery due to their safety profile and their effect on bone mineral density.

Non-medicinal treatments are envisaged in the event of failure of medicinal treatments.

Role of the medicinal product in the care pathway

RYEQO (relugolix / estradiol / norethisterone acetate) is a therapeutic alternative in the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. RYEQO (relugolix / estradiol / norethisterone acetate) had superior efficacy to placebo in terms of reducing fibroid-related bleeding.

In the absence of a study versus a clinically relevant comparator, it is not possible to rank RYEQO (relugolix / estradiol / norethisterone acetate) compared to the other medicinal treatments indicated in fibroid-related menorrhagia and metrorrhagia.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Uterine fibroids are a common condition, causing menometrorrhagia and pelvic pain, and also affecting young women of reproductive age. Fibroids have an impact on quality of life and sexual and reproductive health, and represent the leading cause of hysterectomy in France.
◗ The proprietary medicinal product RYEQO (relugolix / estradiol / norethisterone acetate) is a symptomatic medicinal product.
◗ The efficacy/adverse effects ratio of RYEQO (relugolix / estradiol / norethisterone acetate) is high.
◗ There are alternatives indicated in fibroid related bleeding (see paragraph 05).
◗ RYEQO (relugolix / estradiol / norethisterone acetate) is a first-line treatment.

Public health benefit

Considering:
- the seriousness of the disease and its prevalence/incidence,
- the partially met medical need,
- the lack of additional response to the identified need in the absence of any impact on morbidity and mortality and quality of life,
- the lack of any demonstrated impact on the organisation of care in the absence of data,

RYEQO (relugolix / estradiol / norethisterone acetate) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of RYEQO (relugolix / estradiol / norethisterone acetate) 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 MA indication and at the MA dosages.

◗ **Recommended reimbursement rate: 65%**

Clinical Added Value

Considering,

- demonstration of the superiority of RYEQO (relugolix / estradiol / norethisterone acetate) versus placebo on the percentage of patients with both menstrual blood loss (MBL) volume < 80 mL and an at least 50% reduction from baseline in MBL volume over the last 35 days of treatment (primary endpoint) at 24 weeks,
- the lack of comparative data versus a clinically relevant comparator indicated in fibroid-related menorrhagia, despite the fact that such a comparison would have been possible,
- the absence of robust data concerning a potential effect of RYEQO (relugolix / estradiol / norethisterone acetate) on other fibroid-related symptoms such as pain and reduction in fibroid volume,
- the absence of robust data concerning a potential impact of RYEQO (relugolix / estradiol / norethisterone acetate) on quality of life, despite the fact that this condition has been identified as having an impact on the quality of life and sexual and reproductive health of women,
- the safety profile of RYEQO (relugolix / estradiol / norethisterone acetate), which appears to be favourable, despite the fact that the maximum follow-up period of 104 weeks of treatment only concerned a small sample of 32 patients,

the Transparency Committee considers that RYEQO (relugolix / estradiol / norethisterone acetate) provides no clinical added value (CAV V) in the care pathway for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.