Italian Journal of
Gynæcology & Obstetrics
June 2019 - Vol. 31 - N. 2 - Quarterly - ISSN 2385 - 0868

New implications in the use of Ulipristal acetate for the treatment of uterine fibroids

Attilio Di Spiezio Sardo[1], Antonio Maiorana[2], Maria L. Pisaturo[3], Morena Rocca[4], Carlo Saccardi[5], Stefano Uccella[6], Michele Vignali[7]

[1]Dipartimento di Sanità Pubblica, Università Federico II di Napoli, Italy
[2]Unità Operativa Complessa di Ostetricia e Ginecologia, Ospedale Civico, Palermo, Italy
[3]UOC di Ostetricia e Ginecologia, AOR San Carlo di Potenza, Italy
[4]UO Ginecologia e Ostetricia, Ospedale Giovanni Paolo II, Lamezia Terme, Italy
[5]Unità di Ginecologia e Ostetricia, Dipartimento di Salute della donna e del bambino, Università di Padova, Italy
[6]Dipartimento di Ostetricia e Ginecologia, Ospedale degli Infermi, Biella, Italy
[7]Dipartimento di Scienze Biomediche per la Salute, Università degli Studi di Milano, Ospedale Macedonio Melloni, Italy

ABSTRACT

Ulipristal Acetate (UPA), marketed in Italy with the name of Esmya, is today the only pharmacological treatment with indication for long-term therapy of symptomatic uterine fibroids alternative to surgery. Following the reporting of rare cases of severe liver injury occurring in patients taking Esmya, on 30 November 2017 a safety reassessment procedure was launched for Esmya by the European Medicines Agency (EMA). On 26 July 2018 the procedure ended with the publication of the EMA's final decision confirming the use of the drug in the treatment of symptomatic uterine fibroids, draws some conclusions and puts new indications for the use of the drug. In this point of view the Authors comment on these novel indications and, above all, try to interpret clinically the "non eligibility for surgical treatment" criterion set by the EMA in cases of women with symptomatic uterine fibroid.

Keywords: eligibility, myoma, , surgery, ulipristal acetate.

SOMMARIO

L'UPA, commercializzato in Italia col nome di Esmya, è ad oggi l'unico trattamento farmacologico con indicazione alla terapia a lungo termine dei fibromi uterini sintomatici alternativo alla chirurgia. A seguito della segnalazione di rari casi di grave danno epatico insorti in pazienti che hanno assunto Esmya, il 30 novembre 2017 è stata avviata una procedura di rivalutazione della sicurezza di Esmya da parte dell'Agenzia Europea dei Medicinali (EMA). Il 26 luglio 2018 la procedura si è conclusa con la pubblicazione della decisione finale dell'EMA che conferma l'utilizzazione del farmaco nel trattamento dei fibromi uterini sintomatici, trae alcune conclusioni e pone nuove indicazioni all'utilizzazione del farmaco. In questo articolo gli Autori commentano tali indicazioni e soprattutto tentano di interpretare clinicamente il criterio di "non eleggibilità al trattamento chirurgico" posto dall'EMA nei casi di donne con fibroma uterino sintomatico.

Corresponding Author: Antonio Maiorana
maioran@alice.it

DOI: 10.14660/2385-0868-117

Ulipristal acetate (UPA) was authorised in the European Union in 2012 for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age (who have not reached the menopause). Marketed in Italy under the name Esmya, UPA is currently the only pharmacological treatment with an indication for long-term treatment of symptomatic uterine fibroids as an alternative to surgery. To date, more than 765,000 patients (*IQVIA data, February 2018*) have been treated with Esmya.

Following the reporting of rare cases of severe liver damage in patients taking Esmya, on 30 November 2017, the European Medicines Agency (EMA) commenced a safety review of Esmya. In February 2018, the PRAC (Pharmacovigilance Risk Assessment Committee) adopted temporary, precautionary, restrictive measures, by suspending new prescriptions of the medicinal product and recommending regular liver function monitoring in patients who were still on treatment with Esmya. Having assessed all the preclinical and clinical data available for the medicinal product and having consulted a board of expert hepatologists, the PRAC completed its review in May 2018 and on 1 June of the same year, the EMA's scientific commission (the CHMP) issued its opinion based on the PRAC's recommendations. Lastly, on 26 July 2018, the procedure ended with the publication of the EMA's final decision, which supported that expressed previously by the CHMP[1]

The main conclusions formulated by the abovementioned European Authorities are as follows[1]:

► On the basis of the examined available data, it was not possible either to confirm or to exclude a causal nexus between the use of Esmya and the cases of severe liver damage reported; Esmya may have contributed to the development of certain rare cases of severe liver damage.

► The risk/benefit assessment for Esmya remains favourable and therefore, new prescriptions can once again be issued, taking into account that[2]:

• The use of Esmya is contraindicated in patients with concomitant liver disease

• In patients with an indication for treatment with Esmya, liver function must be regularly monitored before, during and after the end of use of the medicinal product, as instructed in its new SmPC (Summary of Product Characteristics).

► The indications for Esmya have been updated as follows[2]

• Ulipristal acetate is indicated for one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

• Ulipristal acetate is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery.

Both indications have been modified since the initial authorisation of the medicinal product in 2012 and these modifications deserve further investigation.

The former indication (i.e. pre-operative treatment) does not pose any particular problems for the gynaecologist regarding interpretation, and simply states that gynaecologists may prescribe a single course of treatment in order to correct anaemia or reduce the size of a fibroid in order to facilitate subsequent surgery.

Conversely, the latter indication for Esmya (intermittent treatment) has generated considerable puzzlement and a number of requests for clarification from Italian gynaecologists, especially regarding the concept of "non-eligibility" for surgery.

It should be pointed out that, in general, the choice of therapeutic approach for uterine fibroids, be it surgical or medical, must always take into account a vast range of factors that are closely related to both the patient and the medical condition or proposed treatment[3,4]; the cost-effectiveness of each therapy is also an aspect of considerable importance (**Table 1**).

Table 1.
Main factors to be considered when choosing the most suitable medical or surgical treatment in the case of symptoms associated with the presence of uterine myomas

CONDITION-RELATED FACTORS	PATIENT-RELATED FACTORS	PROPOSED PROCEDURE-RELATED FACTORS
• volume and site of uterine fibroids • severity of symptoms • anatomical factors (e.g. hysteroscopy in patients who are virgo) • repeated previous surgery • risk of relapse • comorbidity of myomectomy in women of reproductive age (myometrial defect,increased risk of C/S ....)	• Age • Individual risk factors (obesity, diabetes, hypertension, anaemia, etc.) • Wish to maintain fertility in order to plan a pregnancy in the short- or long-term • Wish to keep the uterus in premenopausal women • Wish to avoid surgery (patient does not want surgery)	• Invasiveness • Costs •Surgical/ medical risks • Anaesthesiological risks

The term "*eleggibile*", which is infrequently used in Italian, derives from a perhaps excessively literal translation of the English term "*eligible*", which appears in the EMA's original document[1].

If we analyse the meaning of "*eligible*" in English, the Oxford dictionary gives the definition "*having the right to do or obtain something; satisfying the appropriate conditions*"[5]. If we translate this concept into surgery, the eligibility of a patient represents a condition of suitability to the surgical procedure, following the assessment of factors associated with the patient, the medical condition and the proposed procedure.

This is where the physician's role necessarily comes into the picture, since it is the doctor who analyses, on the basis of his/her experience and knowledge, the best balance between risks and benefits, between the medical and the surgical approach, making every effort in this analysis to consider not just the costs/benefits or advantages/disadvantages in the short term, but also and above all, in the medium and long term, especially when considering the morbidity and mortality rates for each surgical procedure and, to a lesser extent, medical treatment. It is important to stress that the eligibility criteria for medical or surgical therapy cannot be absolute and that they vary in relation to a number of different factors, whereby a patient with a submucosal uterine fibroid could be eligible for medical therapy for anaemia and subsequently be eligible for a resectoscopic myomectomy for infertility. This goes to show that whatever medical or surgical therapeutic approach is chosen, it is unlikely that it can be restricted to the gloomy confines of a single adjective, rather it must be applied to the individual clinical case in a vast and, above all, perspective scenario.

The choice of the most suitable therapy therefore originates from the interaction between the doctor and the patient; the clinician's decision-making power must take into account disease-specific and patient-specific factors, in order to establish the best risk/benefit balance for that subject[6].

In other words, a patient may be "*ineligible*" or "*unsuitable*" for surgical treatment if the doctor believes that the risks of surgery outweigh its potential benefits or the benefits of medical therapy or even when, quite simply, the woman refuses surgical treatment because she doesn't feel "*it satisfies*" her requirements, preferring other options instead[6].

REFERENCES

1) EMA, Available from: **https://www.ema.europa.eu/medicines/human/referrals/esmya**.
2) **Esmya Summary of Product Characteristics 2018**.
3) Miller CE. **Unmet therapeutics needs for uterine myomas**. J. Minim. Invasive Gynecol. 2009; 16 (1):11-21.
4) Malone LJ. **Myomectomy: recurrence after removal of solitary and multiple myomas**. Obstet. Gynecol. 1969;34:200–209.
5) **Oxford Dictionary**
6) Fernandez H. **Ulipristal acetate and SPRM: A new entity for the therapeutic strategy for symptomatic myomas**. Gynecologie Obstetrique Fertilite´ & Senologie 46 (2018) 671–672