GEDEON RICHTER

ESMYA® (ulipristal acetate): Physician's Guide to Prescribing

SUMMARY

- Esmya® (ulipristal acetate) is indicated for pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.
- The treatment consists of one tablet of 5 mg to be taken orally once daily for up to 3 months. This 3-month treatment course can be repeated once. Re-treatment should start at the earliest during the second menstruation following the first treatment course completion. Treatments should always be started during the first week of menstruation.
- Exclude pregnancy and breastfeeding before prescribing Esmya®.
- Use of Esmya® is contraindicated in cases of genital bleeding of unknown aetiology or for reasons other than uterine fibroids, and in cases of uterine, cervical, ovarian or breast cancer.
- Patients should be informed that treatment with Esmya® usually leads to a significant reduction in menstrual blood loss or amenorrhea within the first 10 days of treatment. Should the excessive bleeding persist, patients should notify their physician.
- Menstrual periods will generally return within 4 weeks after the end of the treatment course.
- Esmya® can cause transient increased thickness of the endometrium.
- If this happens, Esmya® treatment can be continued for a total of up to 3 months.
- Endometrial thickness usually disappears after treatment is stopped and menstruation has occurred but if it persists after this time it should be investigated according to usual practice.
- Esmya® causes reversible changes in the endometrium (called PRM associated endometrial changes, PAEC) in approximately 60% patients.
- If you send a hysterectomy or endometrial biopsy specimen for histological analysis please inform the pathologist that the patient has been pre-treated with Esmya®.

NOTICE TO ALL GYNAECOLOGISTS

Ulipristal acetate belongs to the class of Progesterone Receptor Modulators (PRMs), also known as Selective Progesterone Receptor Modulators (SPRMs) and has a specific pharmacodynamic action on the endometrium. Increase in thickness and reversible histological changes of the endometrium may occur. This Physician's Guide to Prescribing is intended to describe these changes and to propose a schedule for the management of endometrial thickening in clinical practice. The SmPC is provided in attachment to this Physician's Guide to Prescribing.

CONTACT INFORMATION:

Medical Information Service

PregLem S.A.

3, chemin du Pré Fleuri,

1228 Plan-Les-Ouates, Geneva, Switzerland

Email: medicalinformation@preglem.com

Phone: +41 22 884 03 85

CONTENTS

1 INTRODUCTION

Esmya® (ulipristal acetate) is indicated for pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

Ulipristal acetate belongs to the class of Progesterone Receptor Modulators (PRMs), also known as Selective Progesterone Receptor Modulators (SPRMs) and has a specific pharmacodynamic action on the endometrium. Increase in thickness and histological changes of the endometrium may occur.

This Guide is intended to:

- highlight key information you should know about Esmya® treatment,
- describe the above mentioned changes,
- provide a schedule for the management of endometrial thickening in clinical routine.

2 KEY INFORMATION ABOUT THERAPEUTIC INDICATION AND POSOLOGY OF ESMYA®

Esmya® is indicated for pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

The treatment consists of one tablet of 5 mg to be taken orally once daily for up to 3 months. This 3-month treatment course can be repeated once. Re-treatment should start at the earliest during the second menstruation following the first treatment course completion. Treatments should always be started during the first week of menstruation.

Important to Note:

Each treatment course should not exceed 3 months as the risk of adverse impact on the endometrium is unknown if treatment is continued.

Use of Esmya® is contra-indicated during pregnancy; therefore pregnancy and breastfeeding should be excluded prior to administering Esmya®.

3 OCCURENCE OF ENDOMETRIUM THICKENING AND SPECIFIC ENDOMETRIAL HISTOLOGICAL CHANGES (PAEC)

Esmya® (ulipristal acetate) belongs to the class of Progesterone Receptor Modulators (PRMs), also known as Selective Progesterone Receptor Modulators (SPRMs), which express

agonist/antagonist activities based on the target tissue and absence or presence of progesterone[1].

Esmya® has a specific, direct effect on the endometrium. During treatment with Esmya®, an increase in thickness of the endometrium may occur. Furthermore, changes in the histology of the endometrium may be observed in patients treated with Esmya®. These changes are reversible after treatment cessation. These histological changes are denoted as "Progesterone receptor modulator Associated Endometrial Changes" or PAEC.

Each treatment course should not exceed 3 months as the risk of adverse impact on the endometrium is unknown if treatment is continued.

3.1 Esmya® effect on Endometrium and important recommendation

3.1.1 Histological appearances termed PAEC

PAEC is a histological feature characterized by an inactive and weakly proliferating epithelium associated with asymmetry of stromal and epithelial growth resulting in prominent cystically dilated glands with admixed oestrogen (mitotic) and progesterone (secretory) epithelial effects. Such a pattern has been observed in approximately 60% of patients treated with Esmya® for 3 months. These changes are reversible after treatment cessation. These changes should not be confused with endometrial hyperplasia[2,3].

According to Williams *et al*., the key features distinguishing PAEC from proliferative endometrium or hyperplasia are: (a) low mitotic activity; (b) abortive subnuclear vacuoles; (c) apoptosis; and (d) absence of stromal breakdown and glandular crowding. These changes were reported to reverse when ulipristal acetate treatment is stopped and after menstruation return[4].

When sending hysterectomy specimens or endometrial biopsy specimens for histological evaluation, it is important that the pathologist is informed that the patient has been treated with Esmya®.

[1] Chabbert-Buffet N, Mesuri G, Bouchard P, Spitz IM. (2005) Selective progesterone receptor modulators and progesterone antagonists: mechanisms of action and clinical applications. Human Reproduction Update 11; 293-307.

[2] Mutter GL, Bergeron C, Deligdisch L, et al. The spectrum of endometrial pathology induced by progesterone receptor modulators. Mod Pathol 2008;21:591-8.

[3] Olga B Ioffe, Richard J Zaino and George L Mutter, et al. Endometrial changes from short-term therapy with CDB-4124, a selective progesterone receptor modulator. Modern Pathology (2009) 22, 450–459.

[4] Williams AR, Bergeron C, Barlow DH, Ferenczy A. Endometrial Morphology After Treatment of Uterine Fibroids With the Selective Progesterone Receptor Modulator, Ulipristal Acetate. Int J Gynecol Pathol 2012;31(6):556-69.

3.1.2 Endometrium thickness

In pre-menopausal women the thickness of the endometrium varies throughout the menstrual cycle. The monitoring of endometrial thickness in Phase III studies showed that about 3-5% of patients have endometrial thickness >16mm at screening, about 10-15% of patients treated with Esmya® have endometrial thickness > 16mm after 3 months of treatment.
This thickening is asymptomatic and disappears after treatment is withdrawn and menstruation occurs.

Table 1 Endometrium thickness > 16mm

(Data from two Phase III studies, PEARL I and II)

	Placebo	**Esmya® 5mg**	**Esmya® 5mg**	**GnRH-Agonist**
Screening	0	1.1%	5.2%	4.0%
Week 13 (end of treatment)	2.1%	10.5%	11.3%	1.0%
Week 17*	/	/	5.2%	5.1%
Week 26*	0	5.0%	4.1%	4.1%
Week 38*	3.3%	3.3%	5.5%	4.1%

* Week 17, 26 and 38 data only include subjects who did not undergo hysterectomy or endometrium ablation

In subjects with endometrium thickness > 16 mm at week 13 (end of treatment), PAEC features were observed in 90% of patients (Esmya® 5mg).

Considering that the Esmya®-induced endometrium thickening disappears after treatment is withdrawn and menstruation occurs, there is no need to investigate it unless it persists after treatment has stopped and after at least one menstruation has occurred.

4 SCHEDULE FOR THE MANAGEMENT OF ENDOMETRIUM THICKENING

Regular assessment of endometrial thickness in patients undergoing Esmya® treatment is not necessary as increased thickness disappears after treatment cessation and occurrence of menstrual periods and is not associated with any clinical concern.
If an ultrasound is performed during or after Esmya® treatment (e.g. for fibroid volume evaluation) the recommended patient's management is as follows:

4.1 <u>If endometrium thickness > 16 mm during Esmya® treatment:</u>

When endometrium thickness > 16 mm is observed during Esmya® treatment, there is no reason for discontinuation and each treatment course can be continued for up to 3 months.

4.2 If endometrium thickness > 16 mm at the end of Esmya® treatment:

At treatment end, if a patient displays an endometrium thickness > 16 mm, it is likely that it is related to the PAEC. No immediate action is required as this thickening disappears after treatment is withdrawn and menstruation occurs. Should endometrium thickness still exceed 16 mm beyond the 3 months after Esmya® treatment discontinuation and after return of menstruation, standard of care for investigating endometrial thickness in pre-menopausal women should apply to exclude underlying conditions.

5 ADDITIONAL INFORMATION

The prevalence of true simple hyperplasia in the population eligible for ulipristal acetate treatment is low but not negligible. In women between the age of 17 and 50 years old presenting abnormal uterine bleeding, endometrial hyperplasia is estimated to be between 4.3% and 6.7%[5,4]. In these publications simple hyperplasia was observed between 2.0% and 2.3%, complex hyperplasia between 2.3% and 2.9%, and atypical hyperplasia between 0.03% and 1.3%.

There are well established criteria for differentiation between PAEC, hyperplasia and adenocarcinoma:

- In hyperplasia, the dilated glands are lined by epithelium that is stratified and thicker than normal, with frequent mitotic figures, resembling the appearances of the mid to late proliferative phase.

- In PAEC, the glands are also distended, but lined by an inactive epithelium that is thinner than that of the normal proliferative phase, and often appears flattened and atrophic.

- In endometrial adenocarcinoma, the histology is very different from PAEC. The malignant glands are crowded and may be confluent without intervening stroma. There is complexity of gland architecture, often with a cribriform pattern, but gland dilatation is infrequent. The enlarged epithelial cells show frequent atypical mitotic figures, and rounded nuclei with clumped chromatin and prominent nucleoli.

The pathologists have been made aware, in a Pathologist's Guide similar to this one, about the histological differences between PAEC, unopposed oestrogen effect and endometrial hyperplasia, in order to facilitate their appropriate histopathologic endometrial assessment.

[5] Lasmar R. B., Prevalence of hysteroscopic findings and histologic diagnoses in patients with abnormal uterine bleeding. American Society of Reproductive Medicine, 2008; 1803-1807. Vol 89.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare Professionals are asked to report any suspected adverse reactions to **Any suspected adverse drug reactions can be reported as follows:**

Report forms can be downloaded from http://medicinesauthority.gov.mt/adrportal and sent by post or email to;

P: ADR reporting/ 203, level 3 Rue D'ArgensGzira GZR 1368

E: postlicensing.medicinesauthority@gov.mt

or

E: pv@alfredgera.com