

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

SUMMARY

- Esmya[®] (ulipristal acetate) is indicated for pre-operative and intermittent 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 treatment courses of up to 3 months each. Treatments should only be initiated when menstruation has occurred: The first treatment course should start during the first week of menstruation. Re-treatment courses should start at the earliest during the first week of the second menstruation following the previous treatment course completion. The treating physician should explain to the patient the requirement for treatment free intervals. Repeated intermittent treatment has been studied up to 4 intermittent treatment courses.
- 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. If, during repeated intermittent treatment, after the initial reduction in bleeding or amenorrhea, an altered persistent or unexpected bleeding pattern occurs, such as inter-menstrual bleeding, investigation including endometrial biopsy should be performed in order to exclude other underlying conditions, including endometrial malignancy.
- Menstrual periods will generally return within 4 weeks after the end of each treatment course.
- Esmya[®] can cause transient and reversible increased thickness of the endometrium under treatment.
- If this happens, each Esmya[®] treatment course can be continued for up to 3 months.
- Endometrial thickness usually disappears after return of menstruations during off-treatment periods or within 3 months after treatment courses are stopped. In case of repeated intermittent treatment, periodic monitoring of the endometrium is recommended. This includes annual ultrasound to be performed after resumption of menstruation during off-treatment period. If endometrial thickening is noted, which persists after return of menstruations during off-treatment periods or beyond 3 months following the end of treatment courses, and/or an altered bleeding pattern is noted, investigation including endometrial biopsy should be performed in order to exclude other underlying conditions, including endometrial malignancy.
- 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.

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CONTENTS

1	INTRODUCTION.....	4
2	KEY INFORMATION ABOUT THERAPEUTIC INDICATION AND POSODOLOGY OF ESMYA [®]	4
3	OCCURENCE OF ENDOMETRIUM THICKENING AND SPECIFIC ENDOMETRIAL HISTOLOGICAL CHANGES (PAEC)	5
3.1	Esmya [®] effect on Endometrium and important recommendation	5
3.1.1	Histological appearances termed PAEC	5
3.1.2	Endometrium thickness	6
4	SCHEDULE FOR THE MANAGEMENT OF ENDOMETRIUM THICKENING	6
4.1	If endometrium thickness > 16 mm during Esmya [®] treatment:	7
4.2	If endometrium thickness > 16 mm at the end of Esmya [®] treatment:.....	7
5	ADDITIONAL INFORMATION	7

1 INTRODUCTION

Esmya[®] (ulipristal acetate) is indicated for pre-operative and intermittent 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 and intermittent 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 treatment courses of up to 3 months each. Treatments should only be initiated when menstruation has occurred: The first treatment course should start during the first week of menstruation. Re-treatment courses should start at the earliest during the first week of the second menstruation following the previous treatment course completion. The treating physician should explain to the patient the requirement for treatment free intervals. Repeated intermittent treatment has been studied up to 4 intermittent treatment courses.

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[®]. If pregnancy is suspected prior to initiation of a new treatment course, a pregnancy test should be performed.

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 progesterone¹.

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}.

In case of hyperplasia (without atypia), monitoring as per usual clinical practice (e.g. a follow-up control 3 months later) would be recommended. In case of atypical hyperplasia, investigation and management as per usual clinical practice should be performed.

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

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.

were reported to reverse when ulipristal acetate treatment is stopped and after menstruation return⁴.

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[®].

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 the first 3-month treatment course. 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 return of menstruations during off-treatment periods or within 3 months after treatment courses are stopped, there is no need to investigate it unless it persists after these timepoints. In case of repeated intermittent treatment, periodic monitoring of the endometrium is recommended. This includes annual ultrasound to be performed after resumption of menstruation during off-treatment period. If endometrial thickening is noted, which persist after return of menstruations during off-treatment periods or beyond 3 months following the end of treatment courses, and/or an altered bleeding pattern is noted, investigation including endometrial biopsy should be performed in order to exclude other underlying conditions, including endometrial malignancy.

4 SCHEDULE FOR THE MANAGEMENT OF ENDOMETRIUM THICKENING

Increased thickness disappears after treatment cessation and occurrence of menstrual periods and is not associated with any clinical concern. However in case of repeated intermittent treatment, periodic monitoring of the endometrium is recommended. This includes annual ultrasound to be performed after resumption of menstruation during off-treatment period. If endometrial thickening is noted, which persists after return of menstruations during off-treatment periods or beyond 3 months following the end of treatment courses, and/or an altered bleeding pattern is noted, investigation including endometrial biopsy should be performed in order to exclude other underlying conditions, including endometrial malignancy.

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 If endometrium thickness > 16 mm during Esmya[®] treatment:

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:

Under treatment, 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 return of menstruations during off-treatment periods or after treatment courses are withdrawn and menstruation occurs. Should endometrium thickness still exceed 16 mm after return of menstruations during off-treatment periods or beyond the 3 months after Esmya[®] treatment courses discontinuation and after return of menstruation, investigation including endometrial biopsy should be performed in order to exclude other underlying conditions, including endometrial malignancy.

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:

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.

- 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.