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

SUMMARY

- Ulipristal acetate indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women who have not reached menopause when uterine fibroid embolisation and/or surgical treatment options are not suitable or have failed.
- 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.
- Treating physicians should evaluate together with the patient using evidence-based medicine the risks and benefits of all available alternatives to allow patients to take an informed decision.
- During the post-marketing experience, cases of liver injury and hepatic failure, some requiring liver transplantation were reported.
- Liver function tests must now be performed before starting treatment. Treatment must not be initiated if transaminases (alanine transaminase (ALT) or aspartate aminotransferase (AST)) exceed 2 x ULN (isolated or in combination with bilirubin >2 x ULN).
- During treatment, liver function tests must be performed monthly during the first 2 treatment courses. For further treatment courses, liver function must be tested once before each new treatment course and when clinically indicated.
- If a patient during treatment shows signs or symptoms compatible with liver injury (fatigue, asthenia, nausea, vomiting, right hypochondrial pain, anorexia, jaundice), treatment should be stopped, and the patient should be investigated immediately, and liver function tests performed.
- Patients who develop transaminase levels (ALT or AST) > 3 times the upper limit of normal during treatment should stop treatment and be closely monitored.
- In addition, liver testing should be performed 2-4 weeks after each treatment course has stopped.
- Exclude pregnancy and breastfeeding before prescribing Esmya®.
- Use of Esmya® is contraindicated in cases of hypersensitivity to the active substance or to any of the excipients, pregnancy and breastfeeding, genital bleeding of unknown aetiology or for reasons other than uterine fibroids; uterine, cervical, ovarian or breast cancer or in patients with any underlying hepatic disorder.
- 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.
- Each treatment course should each not exceed 3 months as the risk of adverse impact on the endometrium is unknown if treatment is continued without interruption. Repeated intermittent treatment has been studied up to 4 intermittent courses.
- 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. It is also intended to describe the liver monitoring measures and subsequent management of any potential hepatic injury. The SmPC is provided in attachment to this Physician's Guide to Prescribing.

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REPORTING OF SUSPECTED ADVERSE REACTIONS

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie

Adverse events should also be reported to:

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Tel: +44 (0) 207 604 8806

Email: drugsafety.uk@gedeonrichter.eu

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1 INTRODUCTION

Ulipristal acetate is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women who have not reached menopause when uterine fibroid embolisation and/or surgical treatment options are not suitable or have failed.

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,
- detail the liver function monitoring schedule,
- provide a schedule for the management of endometrial thickening in clinical routine.

2 KEY INFORMATION ABOUT THERAPEUTIC INDICATION AND POSOLOGY OF ESMYA®

Ulipristal acetate is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women who have not reached menopause when uterine fibroid embolisation and/or surgical treatment options are not suitable or have failed.

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 with limited safety data having been studied up to 8 intermittent treatment courses.

Treating physicians should evaluate together with the patient using evidence-based medicine the risks and benefits of all available alternatives to allow patients to take an informed decision.

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.

Esmya® is contraindicated in women with known hypersensitivity to the active substance or to any of the excipients listed in the SmPC. Use of Esmya® is contraindicated in cases of underlying hepatic disorder, genital bleeding of unknown aetiology or for reasons other than uterine fibroids. It is also contraindicated in cases of uterine, cervical, ovarian or breast cancer. Use of Esmya® is also contra-indicated during pregnancy and breastfeeding. Pregnancy should be excluded prior to initiating treatment with Esmya®. If pregnancy is suspected prior to initiation of a new treatment course, a pregnancy test should be performed.

3 OCCURRENCE OF HEPATIC INJURY

During the post-marketing experience, cases of liver injury and hepatic failure have been reported. In a small number of these cases, liver transplantation was required.

To further minimize the risk of the patients, an underlying hepatic disorder is now a contraindication to receiving Esmya®. Furthermore, liver function tests must now be performed before starting treatment. Treatment must not be initiated if transaminases (alanine transaminase (ALT) or aspartate aminotransferase (AST)) exceed 2 x ULN (isolated or in combination with bilirubin >2 x ULN).

During treatment, liver function tests must be performed monthly during the first 2 treatment courses. For further treatment courses, liver function must be tested once before each new treatment course and when clinically indicated.

If a patient during treatment shows signs or symptoms compatible with liver injury (fatigue, asthenia, nausea, vomiting, right hypochondrial pain, anorexia, jaundice), treatment should be stopped and the patient should be investigated immediately, and liver function tests performed.
Patients who develop transaminase levels (ALT or AST) > 3 times the upper limit of normal during treatment should stop treatment and be closely monitored.
In addition liver testing should be performed 2-4 weeks after each treatment course has stopped.

4 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.

4.1 Esmya® effect on Endometrium and important recommendation

4.1.1 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 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.

4.1.2 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 of reproductive age experiencing heavy menstrual bleeding 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, -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.
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.

5 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:

5.1 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.

5.2 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.

6 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.

[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 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.

7 GUIDE TO ACTIONS

When	What do I need to do?	Subsequent actions
Before initiating a treatment course	• Ask the woman if it is possible she is pregnant (perform pregnancy test if necessary). • Ask the woman if she is breast feeding. • Exclude presence of uterine, cervical, ovarian or breast cancer, and underlying hepatic disorder. • Exclude pre-operative treatment of uterine fibroids in adult women of reproductive age. • Allow patients to make an informed decision using evidence-based medicine to assess the risks and benefits of all available alternatives. • Explain to women the effects of Esmya® on the endometrium, the importance of treatment-free periods and the requirement for periodic monitoring of the endometrium with intermittent treatment. • Inform women that treatment with Esmya® usually leads to a reduction in menstrual blood loss or amenorrhoea within the first 10 days and to tell their doctor if excessive bleeding persists. • Inform women to tell their doctor if, during repeated intermittent treatment, and after an initial reduction in bleeding or amenorrhea, an altered persistent or unexpected bleeding pattern occurs, such as inter-menstrual bleeding. • Discuss with women the risk of liver injury and the need for liver function monitoring. • Explain to women the signs and symptoms of liver injury and advise them to seek urgent medical attention if they develop these. • Inform women about the Patient Card, where they can obtain a copy and advise them to read it carefully. • Perform liver function tests.	• Do not initiate Esmya® if the woman is pregnant or breast-feeding. • Do not initiate Esmya® in any woman with uterine, cervical or breast cancer. • Do not initiate Esmya® in any woman with underlying liver disorder. • Do not initiate Esmya® in women with baseline alanine transaminase (ALT) or aspartate aminotransferase (AST) more than 2-times the upper limit of normal (ULN) (isolated or in combination with bilirubin more than 2-times ULN). • Do not initiate Esmya® in adult women of reproductive age for pre-operative treatment of uterine fibroids.

When	What do I need to do?	Subsequent actions
During treatment course and/or off-treatment period between courses	• Monitor endometrium periodically including an annual ultrasound of endometrium after resumption of menstruation during off-treatment period. • Perform liver function tests monthly during the first two treatment courses. • For further treatment courses, liver function must be tested once before each new treatment course and when clinically indicated.	• If endometrial thickening persists after return of menstruation during off-treatment periods or beyond 3 months following the end of treatment courses, and/or altered bleeding pattern is noted, investigate, including with endometrial biopsy, to exclude other underlying conditions, including endometrial malignancy. • 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. • When sending hysterectomy specimens or endometrial biopsy specimens for histological evaluation, inform the pathologist that the patient has been treated with Esmya®. • Patients who develop transaminase levels (ALT or AST) > 3 times the upper limit of normal during treatment should stop treatment and be closely monitored. • If a patient during treatment shows signs or symptoms compatible with liver injury (fatigue, asthenia, nausea, vomiting, right hypochondrial pain, anorexia, jaundice), treatment should be stopped, the patient should be investigated immediately and liver function test performed.
2-4 weeks after treatment has stopped	• Perform liver function tests 2 to 4 weeks after cessation of every course of treatment.	• Manage as clinically indicated.