Treating Uterine Fibroids: Medical Management in Practice

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Mr Ertan Saridogan has received honoraria from:
Gedeon Richter
Olympus
Karl Storz
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OBJECTIVES

• The key clinical trial data for ESMYA® as a non-surgical treatment for moderate to severe symptoms of uterine fibroids

• The changes to ESMYA clinical practice in relation to the recent regulatory safety review

• The safety considerations and monitoring requirements to undertake as part of ESMYA patient management
Exploring effects of ESMYA on uterine fibroids

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

ESMYA 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.

The duration of a course of treatment is three months (84 days); subsequent courses should start at the earliest during the second menstruation following completion of the previous treatment course.
CASE STUDY

• 36 year old woman
• History of fibroids
• TCRF 2011 12 fibroids resected
• C/O severe HMB, worse since stopping COC
• Intends to start a family
• US scan: uterus had multiple small fibroids and fibroid seedlings, they were too numerous to count or measure
- Hysteroscopy, at least 20 submucosal fibroids
- F/U in February: Unable to start UPA
- Troublesome HMB
- Restart COC, Tranexamic acid, Mefenamic acid
- Severe bleeding continued, started NET
- Hospital admission
ESMYA HAS BEEN STUDIED IN BOTH CLINICAL AND REAL-WORLD SETTINGS

**PEARL: PGL4001's (UPA's) Efficacy Assessment in Reduction of symptoms due to uterine Leiomyomata**

UPA, ulipristal acetate
PRE-OPERATIVE TREATMENT
PRIMARY AND SECONDARY STUDY ENDPOINTS

Inclusion criteria (N=242):
• Premenopausal women (aged 18–50 years) with uterine myoma(s) (≥1 uterine myoma of ≥3 cm diameter but no myoma >10 cm diameter)
• Excessive uterine bleeding (PBAC score >100 during Days 1–8 of menstruation)
• Anaemia (Haemoglobin ≤10.2 g/dL)
• Eligible for surgical procedure (Hysterectomy, myomectomy, uterine artery embolisation or endometrial ablation)

Primary endpoints
• Demonstrate superior efficacy of UPA + iron versus placebo + iron using:
  – % patients with a reduction in uterine bleeding at week 13 (28-day PBAC score <75)
  – Change in total fibroid volume from screening to week 13 (centralised blinded MRI reading)

Secondary endpoints
• Demonstrate improvements in fibroid-related symptoms e.g.:
  • QoL (Questionnaire assessing fibroid-associated discomfort)
  • Pain (Short-Form McGill Pain Questionnaire)
• Assess the effect of UPA on bleeding patterns (consecutive 28-day PBAC scores)
• Assess the capacity of UPA to induce amenorrhoea (PBAC 28-day score of ≤2; weeks 9 & 13)
• Assess the capacity of UPA to reduce uterine and fibroid volume (% patients with ≤25% reduction)
• Changes in haemoglobin, haematocrit, and ferritin levels

Assess overall safety of UPA in subjects with uterine fibroids

PBAC; Pictorial Blood-loss Assessment Chart; QoL, Quality of life; UPA, ulipristal acetate

PRIMARY AND SECONDARY STUDY ENDPOINTS

Primary endpoint
- Demonstrate non-inferior efficacy of UPA versus a GnRHa (leuprolide acetate) for reducing excessive uterine bleeding due to uterine fibroids prior to surgery (non-inferiority margin: -20%)
  - Proportion of patients with control of uterine bleeding at week 13 (PBAC score <75)

Secondary endpoints
- Demonstrate improvements in fibroid-related symptoms e.g.:
  - QoL (Uterine Fibroid Symptom and Quality of Life questionnaire)
  - Global pain score (Short-Form McGill Pain Questionnaire and visual analogue scale)
- Assess the effect of UPA on bleeding patterns (consecutive 28-day PBAC scores)
- Assess the capacity of UPA to induce amenorrhoea (PBAC 28-day score of ≤2)
- Assess the capacity of UPA to reduce uterine and fibroid volume
- Changes in haemoglobin, haematocrit, and ferritin levels

Assess overall safety of UPA in subjects with uterine fibroids

Inclusion criteria (N=307):
- Premenopausal women (aged 18–50 years) with uterine myoma(s) (≥1 uterine myoma of ≥3 cm diameter but no myoma >10 cm diameter)
- Excessive uterine bleeding (PBAC score >100 during days 1–8 of menstruation)
- Eligible for surgical procedure (hysterectomy, myomectomy, uterine artery embolisation or endometrial ablation)

GnRHa, gonadotrophin-releasing hormone agonist; PBAC, Pictorial Blood-loss Assessment Chart; QoL, quality of life; UPA, ulipristal acetate

ESMYA HAS DEMONSTRATED EFFICACY VS PLACEBO AND NON-INFERIORITY VS GnRHa IN THE REDUCTION OF HEAVY MENSTRUAL BLEEDING¹,²

**PEARL I¹**

*Patients with PBAC <75 at Week 13 (ITT)*

<table>
<thead>
<tr>
<th>Percentage of subjects with PBAC &lt;75</th>
<th>Placebo (N=48)</th>
<th>UPA 5 mg (N=95)</th>
<th>p=0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>18.8%</td>
<td>91.5%</td>
<td></td>
</tr>
</tbody>
</table>

**TIME TO BLEEDING CONTROL† WAS ALSO WITHIN 7 DAYS IN APPROX. 75% OF ESMYA PATIENTS**

**PEARL II²**

*Patients with PBAC <75 at Week 13 (PP)*

<table>
<thead>
<tr>
<th>% of patients with PBAC &lt;75</th>
<th>UPA 5 mg (n=93)</th>
<th>LA 3.75 mg (n=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>90.3%</td>
<td>89.1%</td>
</tr>
</tbody>
</table>

** ESMYA PATIENT TIME TO BLEEDING CONTROL† WAS ALSO MORE RAPID (p<0.0001) THAN GnRHa PATIENTS**

PBAC<75

¹first day for which total PBAC score for all subsequent 28-day periods up to the end of the treatment period was less than 75.

GnRHa, gonadotrophin-releasing hormone agonist; ITT: Intent to treat population; LA: leuprolide acetate; PBAC, Pictorial Bleeding Assessment Chart; PP, Per protocol population; UPA, ulipristal acetate (ESMYA®)

ESMYA HAS DEMONSTRATED EFFICACY VS PLACEBO AND NON-INFERIORITY VS GnRHa IN THE REDUCTION OF FIBROID VOLUME\textsuperscript{1,2}

**PEARL I\textsuperscript{1}**

**Median percentage change in total fibroid volume\textsuperscript{*} at week 13 (ITT)**

- Placebo (N=48)
- UPA 5 mg (N=95)

- Median percentage change in total fibroid volume from screening to Week 13
  - Placebo: -21.2%
  - UPA 5 mg: 3.0%

\textsuperscript{p=0.002}

**ESMYA ALSO SIGNIFICANTLY IMPROVED (p=0.001) DISCOMFORT RELATING TO FIBROIDS VS PLACEBO\textsuperscript{a}**

**Median percentage change in total fibroid volume\textsuperscript{*} at week 13 (ITT)**

- Placebo (N=48)
- UPA 5 mg (N=95)
- LA 3.75 mg (N=93)

- Median % volume reduction in the largest fibroids
  - Placebo: -53%
  - UPA 5 mg: -36%
  - LA 3.75 mg: -36%

**PEARL II\textsuperscript{2}**

**Median percentage change in total fibroid volume\textsuperscript{*} at week 13 (PP)**

- Median % volume reduction in the largest fibroids
  - UPA 5 mg (N=95)
  - LA 3.75 mg (N=93)

- non-inferiority margin: -20%

**ESMYA WAS NON-INFERIOR TO GnRHa IN THE REDUCTION OF FIBROID VOLUME**

\textsuperscript{a}Improvement in median discomfort score due to uterine fibroids at week 13 (ITT)

\textsuperscript{*Volume of 3 largest fibroids combined.}

GnRHa, gonadotrophin-releasing hormone agonist; HRQoL, health-related quality of life; ITT: Intent to treat population; LA: leuprolide acetate; PP, Per protocol population; UPA, ulipristal acetate (ESMYA\textsuperscript{®})

ESMYA HAD TOLERABLE SIDE EFFECTS IN THE PEARL I STUDY

### SAFETY

<table>
<thead>
<tr>
<th>Adverse event (AE)*</th>
<th>Placebo (N=48)</th>
<th>UPA 5 mg (N=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥1 AE</td>
<td>46%</td>
<td>49%</td>
</tr>
<tr>
<td>Headache</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Breast pain / tenderness</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Constipation</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0%</td>
<td>3%</td>
</tr>
</tbody>
</table>

AE, adverse event; UPA, ulipristal acetate

*Adverse events occurring in at least 3% of the patients in any group, with onset at or after the first dose of study drug and on or before the last assessment date of week 17 (4 weeks after the end of the treatment period) are included.

ESMYA HAD A TOLERABLE SAFETY PROFILE AND CAUSED FEWER MENOPAUSAL SYMPTOMS THAN LA DUE TO HIGHER PLASMA OESTRADIOL LEVELS

### SAFETY

<table>
<thead>
<tr>
<th>AEs that occurred in at least 5% of patients in each study group</th>
<th>UPA 5 mg (n=97)</th>
<th>LA 3.75 mg (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥1 AE*</td>
<td>77%</td>
<td>84%</td>
</tr>
<tr>
<td>Moderate to severe hot flushes</td>
<td>11%</td>
<td>40%</td>
</tr>
<tr>
<td>Headache</td>
<td>26%</td>
<td>29%</td>
</tr>
<tr>
<td>Procedural pain</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6%</td>
<td>14%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Anaemia</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Acne</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>Breast pain or tenderness</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

**On average, LA reduced oestradiol levels to within postmenopausal range resulting in a significantly greater proportion of moderate to severe hot flushes (p<0.001)**

AE, adverse event; LA: leuprolide acetate; UPA, ulipristal acetate

*AEs whose start date is on or after the first dose of study drug and on or before the last assessment date of week 17 (4 weeks after end of treatment).

INTERMITTENT TREATMENT
Primary and secondary study endpoints

**Primary endpoint**
- % of patients in amenorrhea at the end of all four treatment courses (1, 2, 3 and 4)
  - Defined as ≤1 day of spotting within a 35-day interval

**Secondary endpoints**
- Time to amenorrhea at the start of each individual treatment course
- Amenorrhea at the end of each treatment course / in the last 56 days of each treatment course
- Controlled bleeding (no episodes of heavy bleeding and maximum 8 days bleeding during last 56-days of treatment course) at the end of all courses / at the end of each course individually
- Volume of the three largest fibroids and uterus
- Demonstrate improvements in fibroid-related symptoms, eg. QoL, pain

**Safety endpoints**
- Number and proportion of patients withdrawing from treatment early for safety reasons
- Number and proportion of patients experiencing adverse events / clinically significant changes

Inclusion criteria (N=451):
- Premenopausal women (aged 18–50 years) with uterine myoma(s) (≥1 uterine myoma of ≥3 cm diameter but no myoma >12 cm diameter)
- Excessive uterine bleeding (PBAC score >100 during days 1–8 of menstruation)
- ELIGIBILITY FOR SURGERY NOT REQUIRED

PBAC, Pictorial Blood Loss Assessment Chart; QoL, quality of life; UPA, ulipristal acetate

ESMYA’S ABILITY TO INDUCE AMENORRHOEA WAS MAINTAINED ACROSS ALL 4 COURSES

UTERINE BLEEDING

Percentage of patients achieving amenorrhea* at the end of each treatment course (PP4)

- COURSE 1 (N=125): 75.8%
- COURSE 2 (N=132): 84.1%
- COURSE 3 (N=152): 86.4%
- COURSE 4 (N=154): 87.5%

Median days to amenorrhea* during each treatment course (PP4)

- COURSE 1 (N=125): 5 days
- COURSE 2 (N=132): 5 days
- COURSE 3 (N=152): 6 days
- COURSE 4 (N=154): 5 days

* Amenorrhea was defined as no more than 1 day of spotting within a 35-day interval.

N, number of patients with non-missing controlled bleeding; n, number of patients with amenorrhea at the end of each treatment course; PP4, Per Protocol Set 4; UPA, ulipristal acetate.

ESMYA HAD A CUMULATIVE EFFECT ON THE REDUCTION OF FIBROID SIZE* ACROSS COURSES

**ESMYA CONTINUED TO REDUCE FIBROID SIZE WITH EACH CONSECUTIVE COURSE; THIS EFFECT WAS MAINTAINED IN THE DRUG-FREE INTERVAL**

*Volume of 3 largest fibroids combined. **After treatment + 1 bleed. † Follow-up 3 months post treatment. PP4; Per Protocol Set 4; UPA, ulipristal acetate

ESMYA PATIENT FIBROID SYMPTOMS WERE CONSISTENT WITH THOSE OF HEALTHY SUBJECTS AT THE END OF 4 COURSES

N, number of patients with non-missing assessments; FAS1, Full Analysis Set 1; UFS-QoL, Uterine Fibroid Symptom and Quality of Life questionnaire; UPA, ulipristal acetate

**SAFETY**

<table>
<thead>
<tr>
<th>AE, No. of patients (%)</th>
<th>Treatment course 1</th>
<th>Treatment course 2</th>
<th>Treatment course 3</th>
<th>Treatment course 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UPA 5 mg (N=230)</td>
<td>UPA 5 mg (N=215)</td>
<td>UPA 5 mg (N=193)</td>
<td>UPA 5 mg (N=180)</td>
</tr>
<tr>
<td>Pts with ≥1 AE</td>
<td>102 (44.3)</td>
<td>59 (27.4)</td>
<td>32 (16.6)</td>
<td>43 (23.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>23 (10.0)</td>
<td>13 (6.0)</td>
<td>4 (2.1)</td>
<td>4 (2.2)</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>13 (5.7)</td>
<td>8 (3.7)</td>
<td>3 (1.6)</td>
<td>5 (2.8)</td>
</tr>
<tr>
<td>Influenza</td>
<td>9 (3.9)</td>
<td>0</td>
<td>1 (0.5)</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2 (0.9)</td>
<td>3 (1.4)</td>
<td>1 (0.5)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (1.3)</td>
<td>4 (1.9)</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (3.5)</td>
<td>0</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Pelvic pain</td>
<td>5 (2.2)</td>
<td>4 (1.9)</td>
<td>1 (0.5)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>6 (2.6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (1.3)</td>
<td>1 (0.5)</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Breast pain</td>
<td>7 (3.0)</td>
<td>2 (0.9)</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>6 (2.6)</td>
<td>1 (0.5)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Note: boxes denote AEs considered to be 'treatment-related'*

**OVERALL AES DECREASED WITH SUBSEQUENT COURSES AND WERE CONSISTENT WITH PREVIOUS PEARL STUDIES**

AE, adverse event; TEAE, Treatment-emergent adverse event; UPA, ulipristal acetate

In all Phase III studies, including repeated intermittent treatment studies, a total of 7 cases of hyperplasia were observed in 789 patients with adequate biopsies (0.89%).

- The vast majority spontaneously reversed to normal endometrium after resumption of menstruation during the off-treatment period.
- The incidence of hyperplasia did not increase with repeated treatment courses.
- The observed frequency is in line with control groups and prevalence reported in literature for symptomatic pre-menopausal women of this age group (mean of 40 years).

These changes are reversible after treatment cessation and should not be confused with endometrial hyperplasia.

The frequency of PAEC did not increase with repeated courses of treatment.

ALL EVIDENCE SO FAR INDICATES PAEC IS HARMLESS AND QUICKLY REVERSIBLE AFTER A COUPLE OF BLEEDS

PATHOLOGISTS DEEMED ENDOMETRIAL CHANGES ELICITED BY ESMYA AS BENIGN

Safety population: All subjects who are enrolled into the study and who receive at least one dose of UPA PAEC, progesterone-receptor-modulator associated endometrial changes; UPA, ulipristal acetate  
NOTE: New WHO Classification of Endometrial Hyperplasias published since the initiation of this study – no plans to reclassify the cases here.

### CONSENSUS RESULTS FROM AT LEAST 2 OF THE 3 PATHOLOGISTS (SAFETY POPULATION)

<table>
<thead>
<tr>
<th>Histology, n (%)</th>
<th>UPA 5 mg (n=230)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>After 2 courses</td>
<td>After 4 courses</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Number of diagnoses</td>
<td>178</td>
<td>148</td>
<td>144</td>
</tr>
<tr>
<td>Benign endometrium</td>
<td>176 (98.9)</td>
<td>147 (99.3)</td>
<td>143 (99.3)</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>1 (0.6)(^a)</td>
<td>1 (0.7)(^b)</td>
<td>1 (0.7)(^b)</td>
</tr>
<tr>
<td>Malignant neoplasm</td>
<td>1*</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) Simple, non-atypical hyperplasia  
\(^b\) Complex, atypical hyperplasia  
* Pre-existing endometrial adenocarcinoma
OVERALL CONCLUSIONS

- UPA 5 mg is an effective and well tolerated dose.\textsuperscript{1-6}
- In patients with moderate to severely symptomatic fibroids, a 12-week course of oral ulipristal acetate 5 mg once daily:\textsuperscript{1-6}
  - controls bleeding and pain
  - reduces fibroid volume compared with baseline
  - restores quality of life compared with baseline
  - has an established safety profile
- Patient benefit has also been confirmed by real-world data of UK ESMYA patients (PREMYA)\textsuperscript{5} and in more racially diverse populations than were analysed in the PEARL studies (VENUS)\textsuperscript{6}

The current licensed posology is 1-course (pre-operative) or multiple courses (intermittent, only in women ineligible for surgery) of 3 months, with off-treatment periods of at least 2 menstrual bleeds.\textsuperscript{7}

Subsequent courses of treatment should commence at the earliest in the second menstrual bleed following completion of the previous course of treatment.\textsuperscript{7}

Regulatory recommendations for ESMYA
HEPATIC EVENTS IN ESMYA PATIENTS LEADING UP TO THE REGULATORY SAFETY REVIEW

~765,000 women exposed to ESMYA by 28 Feb 2018

105 cases referred by physicians and coded as liver-related events

34 cases classified as serious liver disorders by the referring physicians

8 were considered to be severe acute liver injury with Esmya having a possible role as a contributing factor as assessed by the regulatory rapporteurs

4 resulted in liver transplantation

The 1st patient was from Portugal, the 2nd and 3rd patients were from France and the 4th patient was from Germany

EC, European Commission

Cases leading to transplantation:

- **Case 1** (age 55 years) – Early, aspecific symptoms after ESMYA treatment and the histopathological findings of the explanted liver suggest a *pre-existing liver disease*. Could not rule out effects of concomitant medication. Esmya remains as a possible (25-50%) contributing factor.

- **Case 2** (age 58 years) – Pathological examination of the explanted liver suggested a *pre-existing chronic hepatic condition* due to cirrhosis. Esmya remains as a possible contributing factor.

- **Case 3** (age 45 years) – HHV6 detected but role difficult to conclude on. Role of ESMYA is probable, however uncertainties remain.

- **Case 4** age (46 years) – *hepatitis E* and the relatively long latency time are confounding factors. Esmya remains as possible or probable factor.

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REGULATORY SAFETY REVIEW: LIVER CASES

Cases in which patients recovered:

- **Case 5** (age unknown) – *Ibuprofen* as concomitant medication. Some support for a causal relationship between Esmya and liver injury but uncertainty remains due to missing information.

- **Case 6** (age 48 years) – *Sjögren’s syndrome* diagnosed, but uncertainty remains. Causal role of Esmya is considered possible.

- **Case 7** (age 39 years) – Medical history of *Hashimoto’s thyroiditis* and potential confounding factors. The causal role for Esmya is difficult to conclude on, but remains possible.

- **Case 8** (age 48 years) – Computed tomography revealed *Riedel lobe*, but role assessed as less plausible. Causal relationship with Esmya is possible.

Regulatory overall conclusion regarding the role of ESMYA:

- All of the reported cases lacked information hampering causality assessment, and causal relationship with ESMYA and serious hepatic injury is therefore not firmly established.

- There was sufficient information to conclude that a causal association between Esmya and severe liver injury is plausible.

**HHV6, human herpes virus 6**

SUMMARY OF ESMYA REGULATORY SAFETY REVIEW FINDINGS

- No pre-clinical signs of liver toxicity in numerous species
- No signal during clinical trials
- No evidence of the classical mechanisms of liver toxicity in the recent *in vitro* investigations
- Rare cases of liver injury were reported during 6 years post-marketing experience with ESMYA (4 of them required liver transplantation)
- No definitive conclusion on causal relationship can be drawn from the available data
- No risk pattern or patients at risk could be identified

**NEVERTHELESS, THE NUMBER OF CASES WITH SEVERE INJURY LEADING TO LIVER TRANSPLANTATION SHOULD BE CONSIDERED AS A SIGNAL OF POSSIBLE RARE IDIOSYNCRATIC DRUG-INDUCED LIVER INJURY**
CONCLUSIONS OF THE REGULATORY SAFETY REVIEW

The regulatory safety review concluded that ESMYA may have contributed to the development of some cases of serious liver injury and made the following recommendations to reduce the risk:

1. ESMYA must not be used in women with known liver problems.

2. A liver function test should be performed before starting each treatment course and treatment must not be started if liver enzyme levels are more than 2 times the upper limit of normal.

3. Liver function tests should be performed once a month during the first two treatment courses and two to four weeks after stopping treatment. If the test is abnormal (liver enzyme levels more than 3 times the upper limit of normal), the doctor should stop treatment and closely monitor the patient.

4. ESMYA should be used for more than one treatment course only in women who are not eligible for surgery. Women who are about to have surgery should continue to use only one course.

5. A card will be included in the box of the medicine to inform patients about the need for liver monitoring, and to contact their doctor should they develop symptoms of liver injury (such as tiredness, yellowing of the skin, darkening of the urine, nausea and vomiting).

6. Studies should be performed to determine the effects of ESMYA on the liver and whether these measures are effectively minimising the risks.

INTERPRETING THE LICENSED INDICATION

• 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**.

ADDITIONAL MONITORING

Liver function tests:

• Liver function tests must be performed **before starting treatment.** Treatment must not be initiated if transaminases (ALT or AST) exceed $2 \times$ ULN (isolated or in combination with bilirubin $>2 \times$ 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

• In addition, liver testing should be performed **2–4 weeks after treatment has stopped**


ALT, alanine aminotransferase; AST, aspartate aminotransferase; UF, uterine fibroids; ULN, upper limit of normal; UPA, ulipristal acetate
Defining Esmaya Patients Who Are Not Eligible for Surgery

Surgery may, in some circumstances, be a curative treatment for uterine fibroids, but some women may not be eligible.

The impact of surgery and its longer-term implications are important factors to take into account:
- Women with associated risks (i.e. anaemia, obesity, diabetes, hypertension etc.)
- Uncertain impact on fertility
- High recurrence rate after fertility sparing surgery

The patient’s attitudes to surgery are important factors:
- Women who wish to postpone pregnancy but retain their fertility
- Women in reproductive life wishing to avoid surgery
- Pre-menopausal women wishing to preserve their uterus

Medical treatment with Esmaya provides the only licensed long-term alternative in women with moderately to severely symptomatic uterine fibroids for whom surgery is not an option.
Esmya (ulipristal acetate) should be considered for women with fibroids of 3 cm or more in diameter, taking into account the size, location and number of fibroids, and the severity of the symptoms.

If ulipristal acetate is the preferred treatment option, be aware of measures to reduce the risk of rare but serious liver injury:

- discuss the relative benefits and harms of ulipristal acetate with women, including recognising the signs and symptoms of liver injury, to enable an informed decision
- monitor liver function for the first 2 treatment courses, and as clinically indicated, in line with current prescribing guidance.

Pre-treatment with a gonadotrophin-releasing hormone analogue or ulipristal acetate before hysterectomy and myomectomy should be considered if uterine fibroids are causing an enlarged or distorted uterus.

When ulipristal acetate is used for intermittent treatment in women who are not eligible for surgery, for example where the risks of surgery outweigh the benefits or where the woman declines surgical treatment:

- Offer ulipristal acetate 5 mg (up to 4 courses) to women with heavy menstrual bleeding and fibroids of 3 cm or more in diameter, and a haemoglobin level of 102 g per litre or below.
- Consider ulipristal acetate 5 mg (up to 4 courses) for women with heavy menstrual bleeding and fibroids of 3 cm or more in diameter, and a haemoglobin level above 102 g per litre.

When ulipristal acetate is used for intermittent treatment in women who are not eligible for surgery, for example where the risks of surgery outweigh the benefits or where the woman declines surgical treatment:

- Offer ulipristal acetate 5 mg (up to 4 courses) to women with heavy menstrual bleeding and fibroids of 3 cm or more in diameter, and a haemoglobin level of 102 g per litre or below.
- Consider ulipristal acetate 5 mg (up to 4 courses) for women with heavy menstrual bleeding and fibroids of 3 cm or more in diameter, and a haemoglobin level above 102 g per litre.
THANK YOU
Preparations

ESMYA (ulipristal acetate)

Please refer to the SmPC before prescribing.

Presentation: 5mg tablet

Indication: Treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age - one pre-operative treatment course or intermittent treatment in women who are not eligible for surgery.

Dose and administration: Treatment to be initiated and supervised by physicians experienced in the diagnosis and treatment of uterine fibroids. One tablet of 5mg to be taken orally once a day for a maximum of 3 months, starting during first week of menstrual cycle. Re-treatment courses should start at the earliest during the first week of the second menstruation following the previous treatment course completion. Each treatment course should not exceed 3 months. Treatment free intervals are required between courses. Repeated intermittent treatment has been studied for up to 4 intermittent treatment courses.

Please refer to SmPC for missed dose information.

Patients with renal impairment: No dose adjustment in mild to moderate renal impairment. Not recommended for patients with severe renal impairment unless patient is closely monitored.

Children and adolescent under 18 years: No relevant use.


Pregnancy and lactation: Contraindicated during pregnancy and lactation.

Warnings and Precautions: Should only be prescribed after careful diagnosis and pregnancy should be precluded prior to treatment. Use in women with severe asthma insufficiently controlled by oral glucocorticoids is not recommended. Concomitant use of hormonal contraceptives are not recommended hence a non-hormonal contraceptive method should be used. Reversible histological changes of the endometrium: ‘Progestosterone Receptor Modulator Associated Endometrial Changes’ (PAEC) may be observed in patients. Also, reversible thickening of the endometrium may occur (during) treatment. If it persists beyond 3 months following the end of treatment and return of menstruations, and/or an altered bleeding pattern is noted, this may need to be investigated as per usual clinical practice.

Please refer to SmPC for further details on endometrial changes and management of the same.

In case of repeated intermittent treatment, periodic monitoring of the endometrium is recommended. This includes an annual ultrasound to be performed after resumption of menstruation during off-treatment period. Treatment leads to significant reduction in menstrual blood loss within 10 days and patients should notify their physician if heavy bleeding persists. Hepatic injury and hepatic failure cases were reported during post-marketing experience. Liver function tests (LFTs) must be performed before starting treatment: treatment should not be initiated if transaminases exceed 2x upper limit of normal (ULN). During treatment, LFTs must be performed monthly during the first 2 treatment courses. For further courses, LFTs must be done before each new course and when clinically indicated. Patients who show signs and symptoms compatible with liver injury should have the treatment stopped, LFTs performed and the patient investigated immediately. Patients who develop transaminase levels > 3x the ULN during treatment should stop treatment and be closely monitored. LFTs should be performed 2-4 weeks after end of treatment.

Drug interactions: Hormonal contraceptives and progestogens are likely to reduce the efficacy of ulipristal acetate by competitive action on progestosterone receptors, hence co-administration is not recommended. Not recommended for patients receiving moderate or potent CYP3A4 inhibitors or potent CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin, St John’s wort). Co-administration of P-gp substrates (e.g. dabigatran etexilrate, digoxin) should be separated in time by at least 1.5 hours.

Undesirable effects: The following adverse reactions have been reported during first treatment courses: Very Common (≥1/10) Amenorrhea, Endometrial thickening; Common (≥1/100 to <1/10) Headache, Vertigo, Abdominal pain, Nausea, Acne, Musculoskeletal pain, Hot flush, Pelvic pain, Ovarian cyst, Breast tenderness/pain, Fatigue, Weight gain; Uncommon (>1/1000 to <1/100) Drug hypersensitivity, Anxiety, Emotional disorder, Dizziness, Dry mouth, Constipation, Alopecia, Dry skin, Hyperhidrosis, Back pain, Urinary incontinence, Uterine haemorrhage, Metrorrhagia, Genital discharge, Breast discomfort, Oedema, Asthenia, Increase in cholesterol level Increased triglycerides; Rare (≥1/10,000 to <1/1000) Epistaxis, Dyspepsia, Flatulence, Rupture of ovarian cyst, Breast swelling; Frequency not known Hepatic failure, Angioedema.

When comparing repeated treatment courses, overall adverse reaction rates were less frequent in subsequent treatment courses than during the first one and each adverse reaction was less frequent or remained in the same frequency category (except dyspepsia which was classified as uncommon).

Overdose: Limited experience. Single doses of up to 200mg and daily doses of 50mg for 10 consecutive days administered to a limited number of subjects, and no severe or serious adverse reactions were reported.

Special precautions for storage: Keep the blisters in the outer carton to protect from light.

Legal Category: POM

Basic UK NHS cost: £114.13 per pack of 28 tablets

Basic cost: €139.86 per pack of 28 tablets

Marketing Authorisation Numbers: EU/1/12/750/001, EU/1/12/750/002, EU/1/12/750/003, EU/1/12/750/004, EU/1/12/750/005

Marketing Authorisation Holder: Gedeon Richter Plc., Győmrői út 19-21., 1103 Budapest, Hungary

Further information is available from:

Gedeon Richter UK Ltd, 127 Shirland Road, London W9 2EP. Tel: +44 (0) 207 604 8806.

Email: medinfo.uk@gedeonrichter.eu

Date of Authorisation: 27th of May 2015

Date of Preparation: 26th of July 2018

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.

Adverse events should also be reported to Women’s Health Division of Gedeon Richter (UK) Ltd on 0207 604 8806 or drugsafety.uk@gedeonrichter.eu

Adverse events should be reported to the 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 Women’s Health Division of Gedeon Richter (UK) Ltd on +44 (0) 207 604 8806 or drugsafety.uk@gedeonrichter.eu