ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Esmya 5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of ulipristal acetate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
White to off-white, round biconvex tablet of 7 mm engraved with “ES5” on one face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology
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.
Due to the lack of long term safety data, the duration of treatment should not exceed two treatment courses of 3 months.

If a patient misses a dose, the patient should take ulipristal acetate as soon as possible. If the dose was missed by more than 12 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

Special population
Renal impairment
No dose adjustment is recommended in patients with mild or moderate renal impairment. In the absence of specific studies, ulipristal acetate is not recommended in patients with severe renal impairment unless the patient is closely monitored (see sections 4.4 and 5.2).

Hepatic impairment
No dose adjustment is recommended for patients with mild hepatic impairment. In the absence of specific studies, ulipristal acetate is not recommended in patients with moderate or severe hepatic impairment unless the patient is closely monitored (see sections 4.4 and 5.2).

Paediatric population
There is no relevant use of ulipristal acetate in the paediatric population. The safety and efficacy of ulipristal acetate was only established in women of 18 years and older.

Method of administration
Tablets may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Pregnancy and breastfeeding.
Genital bleeding of unknown aetiology or for reasons other than uterine fibroids.
Uterine, cervical, ovarian or breast cancer.

4.4 Special warnings and precautions for use

Ulipristal acetate should only be prescribed after careful diagnosis. Pregnancy should be precluded prior to treatment.

Contraception
Concomitant use of progestagen-only pills, a progestagen-releasing intrauterine device or combined oral contraceptive pills is not recommended (see sections 4.5). Although a majority of women taking a therapeutic dose of ulipristal acetate have anovulation, a non hormonal contraceptive method is recommended during treatment.

Renal impairment
Renal impairment is not expected to significantly alter the elimination of ulipristal acetate. In the absence of specific studies, ulipristal acetate is not recommended for patients with severe renal impairment unless the patient is closely monitored (see section 4.2).

Hepatic impairment
There is no therapeutic experience with ulipristal acetate in patients with hepatic impairment. Hepatic impairment is expected to alter the elimination of ulipristal acetate, resulting in increased exposure (see section 5.2). This is considered not to be clinically relevant for patients with mildly impaired liver function. Ulipristal acetate is not recommended for use in patients with moderate or severe hepatic impairement unless the patient is closely monitored (see section 4.2).

Concomitant treatments
Co-administration of moderate (e.g. erythromycin, grapefruit juice, verapamil) or potent (e.g. ketoconazole, ritonavir, nefazodone, itraconazole, telithromycin, clarithromycin) CYP3A4 inhibitors and ulipristal acetate is not recommended (see section 4.5).

Concomitant use of ulipristal acetate and potent CYP3A4 inducers (e.g. rifampicin, rifabutin, carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, primidone, St John´s wort, efavirenz, nevirapine, long term use of ritonavir) is not recommended (see section 4.5).

Asthma patients
Use in women with severe asthma insufficiently controlled by oral glucocorticoids is not recommended.

Endometrial changes
Ulipristal acetate has a specific pharmacodynamic action on the endometrium. Increase in thickness of the endometrium may occur. If the endometrial thickening persists beyond 3 months following the end of treatment and return of menstruations, this may need to be investigated as per usual clinical practice to exclude underlying conditions.
Changes in the histology of the endometrium may be observed in patients treated with ulipristal acetate. These changes are reversible after treatment cessation.
These histological changes are denoted as “Progesterone Receptor Modulator Associated Endometrial Changes” (PAEC) and should not be mistaken for endometrial hyperplasia (see sections 4.8 and 5.1).

Only two treatment courses are recommended. The two treatment courses should each not exceed 3 months as the risk of adverse impact on the endometrium is unknown if treatment is continued.

Bleeding pattern
Patients should be informed that treatment with ulipristal acetate 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.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to affect ulipristal acetate:

Hormonal contraceptives
Ulipristal acetate has a steroid structure and acts as a selective progesterone receptor modulator with predominantly inhibitory effects on the progesterone receptor. Thus hormonal contraceptives and progestagens are likely to reduce ulipristal acetate efficacy by competitive action on the progesterone receptor. Therefore concomitant administration of medicinal products containing progestagen is not recommended (see section 4.4 and 4.6).

CYP3A4 inhibitors
Following administration of the moderate CYP3A4 inhibitor erythromycin propionate (500 mg twice daily for 9 days) to healthy female volunteers, C_{max} and AUC of ulipristal acetate increased 1.2 and 2.9 fold, respectively; the AUC of the active metabolite of ulipristal acetate increased 1.5 fold while the C_{max} of the active metabolite decreased (0.52 fold change).

Following administration of the potent CYP3A4 inhibitor ketoconazole (400 mg once daily for 7 days) to healthy female volunteers, C_{max} and AUC of ulipristal acetate increased 2 and 5.9 fold, respectively; the AUC of the active metabolite of ulipristal acetate increased 2.4 fold while the C_{max} of the active metabolite decreased (0.53 fold change).

No dose adjustment is considered necessary for administration of ulipristal acetate to patients receiving concomitant mild CYP3A4 inhibitors. Co-administration of moderate or potent CYP3A4 inhibitors and ulipristal acetate is not recommended (see section 4.4).

CYP3A4 inducers
Administration of the potent CYP3A4 inducer rifampicin (300 mg twice daily for 9 days) to healthy female volunteers markedly decreased C_{max} and AUC of ulipristal acetate and its active metabolite by 90 % or more and decreased ulipristal acetate half-life by 2.2-fold corresponding to an approximately 10-fold decrease of ulipristal acetate exposure. Concomitant use of ulipristal acetate and potent CYP3A4 inducers (e.g. rifampicin, rifabutin, carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, primidone, St John´s wort, efavirenz, nevirapine, long term use of ritonavir) is not recommended (see section 4.4).

Medicinal products affecting gastric pH
Administration of ulipristal acetate (10 mg tablet) together with the proton pump inhibitor esomeprazole (20 mg daily for 6 days) resulted in approximately 65% lower mean C_{max}, a delayed t_{max} (from a median of 0.75 hours to 1.0 hours) and 13% higher mean AUC. This effect of medicinal products that increase gastric pH is not expected to be of clinical relevance for daily administration of ulipristal acetate tablets.

Potential for ulipristal acetate to affect other medicinal products:

Hormonal contraceptives
Ulipristal acetate may interfere with the action of hormonal contraceptive products (progestagen only, progestagen releasing devices or combined oral contraceptive pills) and progestagen administered for other reasons. Therefore concomitant administration of medicinal products containing progestagen is not recommended (see sections 4.4 and 4.6). Medicinal products containing progestagen should not be

taken within 12 days after cessation of ulipristal acetate treatment.

P-gp substrates
In vitro data indicate that ulipristal acetate may be an inhibitor of P-gp at clinically relevant concentrations in the gastrointestinal wall during absorption.
Simultaneous administration of ulipristal acetate and a P-gp substrate has not been studied and an interaction cannot be excluded. *In vivo* results show that ulipristal acetate (administered as a single 10 mg tablet) 1.5 hour before administration of the P-gP substrate fexofenadine (60 mg) has no clinically relevant effects on the pharmacokinetic of fexofenadine. It is therefore recommended that co-administration of ulipristal acetate and P-gp substrates (e.g. dabigatran etexilate, digoxin, fexofenadine) should be separated in time by at least 1.5 hours.

4.6 Fertility, pregnancy and lactation

Contraception in females
Ulipristal acetate is likely to adversely interact with progestagen-only pills, progestagen-releasing devices or combined oral contraceptive pills, therefore, concomitant use is not recommended. Although a majority of women taking a therapeutic dose of ulipristal acetate have anovulation, a non hormonal contraceptive method is recommended during treatment (see sections 4.4 and 4.5).

Pregnancy
Ulipristal acetate is contraindicated during pregnancy (see section 4.3).
There are no or limited amount of data from the use of ulipristal acetate in pregnant women. Although no teratogenic potential was observed, animal data are insufficient with regard to reproduction toxicity (see section 5.3).

Breast-feeding
Available toxicological data in animals have shown excretion of ulipristal acetate in milk (for details see section 5.3). Ulipristal acetate is excreted in human milk. The effect on newborn/infants has not been studied. A risk to the newborns/infants cannot be excluded. Ulipristal acetate is contraindicated during breast-feeding (see sections 4.3 and 5.2).

Fertility
A majority of women taking a therapeutic dose of ulipristal acetate have anovulation, however, the level of fertility while taking multiple doses of ulipristal acetate has not been studied.

4.7 Effects on ability to drive and use machines

Ulipristal acetate may have minor influence on the ability to drive or use machines as mild dizziness has been observed after ulipristal acetate intake.

4.8 Undesirable effects

Summary of the safety profile
The safety of ulipristal acetate has been evaluated in 602 women with uterine fibroids treated with 5 mg or 10 mg ulipristal acetate during Phase III studies. The most common finding in clinical trials was amenorrhea (80.8%), which is considered as a desirable outcome for the patients (see section 4.4).
The most frequent adverse reaction was hot flush. The vast majority of adverse reactions were mild and moderate (93.6%), did not lead to discontinuation of the medicinal product (99.5%) and resolved spontaneously.
The safety of two intermittent treatment courses (each limited to 3 months) has been evaluated in 131 women with uterine fibroids treated with 10 mg ulipristal acetate in a phase III study and demonstrated a similar safety profile to that observed for one treatment course.

Tabulated list of adverse reactions

Based on pooled data from three phase III studies in patients with uterine fibroids treated for 3 months, the following adverse reactions have been reported. Adverse reactions listed below are classified according to frequency and system organ class. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from available data).

System Organ Class	**Adverse reactions**		
	Very common	**Common**	**Uncommon**
Psychiatric disorders			Anxiety Emotional disorder
Nervous system disorders		Headache*	Dizziness
Ear and labyrinth disorders		Vertigo	
Respiratory, thoracic and mediastinal disorders			Epistaxis
Gastrointestinal disorders		Abdominal pain Nausea	Dyspepsia Dry mouth Flatulence Constipation
Skin and subcutaneous tissue disorders		Acne Hyperhidrosis	Alopecia** Dry skin
Musculoskeletal and connective tissue disorders		Musculoskeletal pain	Back pain
Renal and urinary disorders			Urinary incontinence
Reproductive system and breast disorders	Amenorrhea Endometrial thickening*	Uterine haemorrhage* Hot flush* Pelvic pain Ovarian cyst* Breast tenderness/pain	Metrorrhagia Ovarian cyst ruptured Genital discharge Breast swelling Breast discomfort
General disorders and administration site conditions		Oedema Fatigue	Asthenia
Investigations		Blood cholesterol increased	Blood triglycerides increased Weight increased

* see section "Description of selected adverse reactions"

** The verbatim term “mild hair loss” was coded to the term “alopecia”

Description of selected adverse reactions

Endometrial thickening

In 10-15% of patients, thickening of the endometrium (> 16 mm by ultrasound or MRI at end of treatment) was observed with ulipristal acetate; this reverses when treatment is stopped and menstrual periods resume.

In addition, reversible changes to the endometrium are denoted PAEC and are different from endometrial hyperplasia. If hysterectomy or endometrial biopsy specimens are sent for histology, then

the pathologist should be informed that the patient has taken ulipristal acetate (see sections 4.4 and 5.1).

Hot flush
Hot flushes were reported by 9.8% patients but the rates varied across trials. In the active comparator controlled study the rates were 24% (10.5% moderate or severe) for ulipristal acetate and 60.4% (39.6% moderate or severe) for leuprorelin-treated patients. In the placebo-controlled study, the rate of hot flushes was 1.0% for ulipristal acetate and 0% for placebo. In the open-label phase III clinical trial, the frequency was 4.3% for ulipristal acetate.

Headache
Mild or moderate severity headache was reported in 6.8% of patients.

Ovarian cyst
Functional ovarian cysts were observed during and after treatment in 1.2% of patients and in most of the cases spontaneously disappeared within a few weeks.

Uterine haemorrhage
Patients with heavy menstrual bleeding due to uterine fibroids are at risk of excessive bleeding, which may require surgical intervention. A few cases have been reported during ulipristal acetate treatment or within 2-3 months after ulipristal acetate treatment was stopped.

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 the national reporting system listed in Appendix V.

4.9 Overdose

Experience with ulipristal acetate overdose is limited.
Single doses up to 200 mg and daily doses of 50 mg for 10 consecutive days were administered to a limited number of subjects, and no severe or serious adverse reactions were reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, progesterone receptor modulators. ATC code: G03XB02.

Ulipristal acetate is an orally-active synthetic selective progesterone receptor modulator characterised by a tissue-specific partial progesterone antagonist effect.

Endometrium
Ulipristal acetate exerts a direct effect on the endometrium. When daily administration of a 5 mg dose is commenced during a menstrual cycle most subjects (including patients with myoma) will complete their first menstruation but will not menstruate again until after treatment is stopped. When ulipristal acetate treatment is stopped, menstrual cycles generally resume within 4 weeks.

The direct action on the endometrium results in class-specific changes in histology termed PAEC. Typically, the histological appearance is 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 progestin (secretory) epithelial effects. Such a pattern has been observed in approximately 60% of patients treated with ulipristal acetate for 3 months. These changes

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

About 5% of patients of reproductive age experiencing heavy menstrual bleeding have an endometrial thickness of greater than 16 mm. In about 10-15% of patients treated with ulipristal acetate the endometrium may thicken (> 16 mm) during treatment. This thickening disappears after treatment is withdrawn and menstruation occurs. If endometrial thickness persists beyond the 3 months following the end of treatment and return of menstruations then this may need to be investigated as per usual clinical practice to exclude underlying conditions.

Fibroids
Ulipristal acetate exerts a direct action on fibroids reducing their size through inhibition of cell proliferation and induction of apoptosis.

Pituitary
A daily dose of ulipristal acetate 5 mg inhibits ovulation in the majority of patients as indicated by progesterone levels maintained at around 0.3 ng/ml.

A daily dose of ulipristal acetate 5 mg partially suppresses FSH levels but serum oestradiol levels are maintained in the mid-follicular range in the majority of patients and are similar to levels in patients who received placebo.

Ulipristal acetate does not affect serum levels of TSH, ACTH or prolactin during 3 months of treatment.

Clinical efficacy and safety
The efficacy of fixed doses of ulipristal acetate 5 mg and 10 mg once daily was evaluated in two Phase 3 randomised, double-blind, 13 week studies recruiting patients with very heavy menstrual bleeding associated with uterine fibroids. Study 1 was double-blind placebo controlled. Patients in this study were required to be anaemic at Study entry (Hb < 10.2 g/dl) and all patients were to receive oral iron 80 mg Fe++ in addition to study drug. Study 2 contained the active comparator, leuprorelin 3.75 mg given once per month by intramuscular injection. In Study 2, a double-dummy method was used to maintain the blind. In both studies menstrual blood loss was assessed using the Pictorial Bleeding Assessment Chart (PBAC). A PBAC >100 within the first 8 days of menses is considered to represent excessive menstrual blood loss.

In study 1, a statistically significant difference was observed in reduction in menstrual blood loss in favour of the patients treated with ulipristal acetate compared to placebo (see Table 1 below), resulting in faster and more efficient correction of anaemia than iron alone. Likewise, patients treated with ulipristal acetate had a greater reduction in myoma size, as assessed by MRI.

In study 2, the reduction in menstrual blood loss was comparable for the patients treated with ulipristal acetate and the gonadotrophin releasing hormone-agonist (leuprorelin). Most patients treated with ulipristal acetate stopped bleeding within the first week of treatment (amenorrhea).
The size of the three largest myomas was assessed by ultrasound at the end of treatment (Week 13) and for another 25 weeks without treatment in patients who did not have hysterectomy or myomectomy performed. Myoma size reduction was generally maintained during this follow-up period in patients originally treated with ulipristal acetate but some re-growth occurred in patients treated with leuprorelin.

Table 1: Results of primary and selected secondary efficacy assessments in Phase III studies

Parameter	Study 1			Study 2		
	Placebo **N = 48**	**Ulipristal acetate 5 mg/day** **N = 95**	**Ulipristal acetate 10 mg/day** **N = 94**	**Leuprorelin 3.75 mg/ month** **N = 93**	**Ulipristal acetate 5 mg/day** **N = 93**	**Ulipristal acetate 10 mg/day** **N = 95**
Menstrual bleeding						
Median PBAC at baseline	376	386	330	297	286	271
Median change at week 13	-59	**-329**	**-326**	-274	-268	-268
Patients in **amenorrhea** at week 13	3 (6.3%)	**69 (73.4%)**[1]	**76 (81.7%)**[2]	74 (80.4%)	70 (75.3%)	85 (89.5%)
Patients whose menstrual bleeding became normal (PBAC < 75) at week 13	9 (18.8%)	**86 (91.5%)**[1]	**86 (92.5%)**[1]	82 (89.1%)	84 (90.3%)	93 (97.9%)
Median change in **myoma volume** from baseline to week 13[a]	+3.0%	**-21.2%**[3]	**-12.3%**[4]	-53.5%	-35.6%	-42.1%

[a] In Study 1, change from baseline in total myoma volume was measured by MRI. In Study 2, change in the volume of the three largest myomas was measured by ultrasound. Bold values in shaded squares indicate that there was a significant difference in the comparisons between ulipristal acetate and the control. These were always in favour of ulipristal acetate.
P values: [1] = <0.001, [2] = 0.037, [3]= <0.002, [4] = <0.006.

In a phase III study in 131 women with uterine fibroids receiving two intermittent 3-month treatment courses of ulipristal acetate 10 mg, amenorrhea was achieved at the end of the first treatment course in 79.5% of subjects. The second treatment course provided comparable results (88.5% of subjects). Myoma volume reduction (mean [median] change from screening) observed during the first treatment course (-41.9% [-49.9%]) was maintained during the second one (-43.7% [-63.2%]). In view of studies 1 and 2 results, it is expected that similarly to the 10 mg dose the efficacy of the 5 mg dose in the first treatment course will be maintained in the second treatment course.
Although the number of patients that completed the four treatment courses of 3 months is limited, i.e. 99 patients, the safety data are sufficient to support one additional 3-month treatment course in a pre-operative setting.

The European Medicines Agency has waived the obligation to submit the results of studies with Esmya in all subsets of the paediatric population in leiomyoma of uterus (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Following oral administration of a single dose of 5 or 10 mg, ulipristal acetate is rapidly absorbed, with a C_{max} of 23.5 ± 14.2 ng/ml and 50.0 ± 34.4 ng/ml occurring approximately 1 h after ingestion, and with an $AUC_{0-\infty}$ of 61.3 ± 31.7 ng/ml 134.0 ± 83.8 ng.h/ml, respectively. Ulipristal acetate is rapidly transformed into a pharmacologically active metabolite with a C_{max} of 9.0 ± 4.4 ng/ml and 20.6 ± 10.9 ng/ml also occurring approximately 1 h after ingestion, and with an $AUC_{0-\infty}$ of 26.0 ± 12.0 ng/ml and 63.6 ± 30.1 ng.h/ml respectively.

Administration of ulipristal acetate (30 mg tablet) together with a high-fat breakfast resulted in approximately 45% lower mean C_{max}, a delayed t_{max} (from a median of 0.75 hours to 3 hours) and 25% higher mean $AUC_{0-\infty}$ compared with administration in the fasted state. Similar results were obtained for the active mono-N-demethylated metabolite. This kinetic effect of food is not expected to be of clinical relevance for daily administration of ulipristal acetate tablets.

Distribution
Ulipristal acetate is highly bound (>98%) to plasma proteins, including albumin, alpha-l-acid glycoprotein, high density lipoprotein and low density lipoprotein.

Ulipristal acetate and its active mono-N-demethylated metabolite are excreted in breast milk with a mean AUCt milk/plasma ratio of 0.74 ± 0.32 for ulipristal acetate.

Biotransformation/Elimination
Ulipristal acetate is readily converted to its mono-N-demethylated and subsequently to its di-N-demethylated metabolites. *In vitro* data indicate that this is predominantly mediated by the cytochrome P450 3A4 isoform (CYP3A4). The main route of elimination is through faeces and less than 10% is excreted in the urine. The terminal half-life of ulipristal acetate in plasma following a single dose of 5 or 10 mg is estimated to be about 38 hours, with a mean oral clearance (CL/F) of about 100 l/h.

In vitro data indicate that ulipristal acetate and its active metabolite do not inhibit CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4, or induce CYP1A2 at clinically relevant concentrations. Thus administration of ulipristal acetate is unlikely to alter the clearance of medicinal products that are metabolised by these enzymes.

In vitro data indicate that ulipristal acetate and its active metabolite are not P-gp (ABCB1) substrates.

Special populations
No pharmacokinetic studies with ulipristal acetate have been performed in women with impaired renal or hepatic function. Due to the CYP-mediated metabolism, hepatic impairment is expected to alter the elimination of ulipristal acetate, resulting in increased exposure (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity.

Most findings in general toxicity studies were related to its action on progesterone receptors (and at higher concentrations on glucocorticoid receptors), with antiprogesterone activity observed at exposures similar to therapeutic levels. In a 39 week study in cynomolgus monkeys, histological changes resembling PAEC were noted at low doses.

Due to its mechanism of action, ulipristal acetate has an embryolethal effect in rats, rabbits (at repeated doses above 1 mg/kg), guinea pigs and in monkeys. The safety for a human embryo is unknown. At doses which were low enough to maintain gestation in the animal species, no teratogenic potential was observed.

Reproduction studies performed in rats at doses giving exposure in the same range as the human dose have revealed no evidence of impaired fertility due to ulipristal acetate in treated animals or the offspring of treated females.

Carcinogenicity studies (in rats and mice) showed that ulipristal acetate is not carcinogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Mannitol
Croscarmellose sodium
Talc
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Keep the blisters in the outer carton in order to protect from light.

6.5 Nature and contents of container

Alu-PVC/PE/PVDC blister.
Pack of 28 and 84 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/750/001
EU/1/12/750/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 February 2012

10. DATE OF REVISION OF THE TEXT

DD/MM/YYYY

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Cenexi
17, Rue de Pontoise
FR-95520 Osny
France

Gedeon Richter Plc,
1103 Budapest
Gyömrői út 19-21
Hungary

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as a result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch of the product in each Member State, the Marketing Authorisation Holder shall agree the content and format of the educational material with the national competent authority.

The Marketing Authorisation Holder (MAH) shall ensure that, at launch and thereafter, all prescribers of Esmya and pathologists who review samples from Esmya-treated patients are provided with educational material.
The educational material shall consist of the following:

- Educational material for prescribers (gynaecologists) which contains:
  - Cover letter
  - SmPC
  - Physician's guide to prescribing Esmya
- Educational material for pathologists which contains
  - Pathologist's guide
  - USB stick or CD ROM with images of digital specimens (digital library with high resolution images).
  - SmPC

The educational material shall contain the following key elements:

Physician's guide to prescribing

- detailed recommendations for management of endometrial thickening
- reminder of the effect of ulipristal acetate on the endometrium
- the need to inform the pathologist that patients were treated with Esmya if biopsy/surgical samples are to be sent for analysis.
- the indication: pre-operative treatment
- the posology: 5 mg tablet 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.
- the contraindications of pregnancy and breastfeeding, genital bleeding of unknown aetiology or for reasons other than uterine fibroids, and uterine, cervical, ovarian or breast cancer.
- absence of safety data on the endometrium for continuous treatment longer than 3 months
- the need to investigate as per usual clinical practice persistence of endometrial thickening following treatment discontinuation and return of menstruation to exclude underlying conditions.

Educational material for pathologists

- key effects of Esmya on Progesterone Receptor Modulator Associated Endometrial Changes (PAEC) and how they differ from those of unopposed oestrogen
- the differential diagnosis between PAEC, unopposed oestrogen and endometrial hyperplasia.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Esmya 5 mg tablets
Ulipristal acetate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg of ulipristal acetate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 tablets
84 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the blisters in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/750/001 28 tablets
EU/1/12/750/002 84 tablets

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Esmya

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Esmya 5 mg tablets
Ulipristal acetate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Gedeon Richter

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Esmya 5 mg tablets
Ulipristal acetate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Esmya is and what it is used for

Esmya contains the active substance ulipristal acetate. It is used to treat moderate to severe symptoms of uterine fibroids (commonly known as myomas), which are non-cancerous tumours of the uterus (womb).
Esmya is used in adult women (over 18 years of age) before they reach the menopause who need an operation for their fibroids.

In some women, uterine fibroids may cause heavy menstrual bleeding (your 'period'), pelvic pain (discomfort in the belly) and create pressure on other organs.

This medicine acts by modifying the activity of progesterone, a naturally occuring hormone in the body. It is used for a maximum of 3 months continuously (this 3-month treatment can be repeated once) to reduce the size of fibroids, to stop or reduce bleeding and to increase your red blood cell count, before the operation.

2. What you need to know before you take Esmya

You should know that most women have no menstrual bleeding (period) during the treatment and for a few weeks afterwards.

Do not take Esmya:
- if you are allergic to ulipristal acetate or any of the other ingredients of Esmya (listed in section 6).
- if you are pregnant or if you are breastfeeding.
- if you have vaginal bleeding not caused by uterine fibroids.
- if you have cancer of the uterus (womb), cervix (the neck of the womb), ovary or breast.

Warnings and precautions:
- If you are currently taking hormonal contraception (for example birth control pills) (see "Other medicines and Esmya") you should use an alternative reliable barrier contraceptive method (such as a condom) while taking Esmya.

- If you have liver or kidney disease tell your doctor or pharmacist before taking Esmya.
- If you suffer from severe asthma, treatment with Esmya may not be suitable for you. You should discuss this with your doctor.

Treatment with Esmya usually leads to a significant reduction or may even stop your menstrual bleeding (your 'period') within the first 10 days of treatment. However, if you continue to experience excessive bleeding tell your doctor.

Your period should generally return within 4 weeks after treatment with Esmya is stopped. The lining of the uterus may thicken or change as a result of taking Esmya. These changes return to normal after treatment is stopped and your periods restart.

Children and adolescents
Esmya should not be taken by children under 18 years of age.

Other medicines and Esmya
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Tell your doctor or pharmacist if you are taking any of the medicines listed below, as these medicines can affect Esmya or be affected by Esmya:
- Certain medicines which are used to treat the heart (e.g. digoxin).
- Certain medicines used to prevent strokes and blood clots (e.g. dabigatran etexilate).
- Certain medicines used to treat epilepsy (e.g. phenytoin, fosphenytoin, phenobarbital, carbamazepine, oxcarbazepine, primidone).
- Certain medicines used to treat HIV infection (e.g. ritonavir, efavirenz, nevirapine).
- Medicines used to treat certain bacterial infections (e.g. rifampicin, telithromycin, clarithromycin, erythromycin, rifabutin).
- Certain medicines to treat fungal infections (e.g. ketoconazole (except shampoo), itraconazole).
- Herbal remedies containing St John's wort (*Hypericum perforatum*) used for depression or anxiety.
- Certain medicines used to treat depression (e.g. nefazodone).
- Certain medicines used to treat hypertension (e.g. verapamil).

Esmya is likely to make some hormonal contraceptives less effective. In addition, hormonal contraceptives and progestagens (e.g. norethindrone or levonorgestrel) are also likely to make Esmya less effective. Therefore, hormonal contraceptives are not recommended and you should use an alternative reliable barrier contraceptive method, such as a condom, during Esmya treatment.

Esmya with food and drink
You should avoid drinking grapefruit juice while on treatment with Esmya.

Pregnancy and breast-feeding
Do not take Esmya if you are pregnant. Treatment whilst pregnant might affect your pregnancy (it is not known if Esmya might harm your baby or whether can cause miscarriage). If you do become pregnant during Esmya treatment, you should stop taking Esmya immediately and contact your doctor or pharmacist.

Esmya is likely to make some hormonal contraceptives less effective (see "Other medicines and Esmya").
Esmya passes into the breast milk. Therefore, do not breast-feed your baby while taking Esmya.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Esmya may cause mild dizziness (see section 4 “Possible side effects”). Do not drive or use machines if you experience these symptoms.

3. How to take Esmya

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
The recommended dose is one 5 mg tablet per day, for up to 3 months. This 3-month treatment can be repeated once. If you have been prescribed a second course of Esmya 3-month treatment, you should start it at the earliest during the second menstrual period following the first treatment completion.
You should always start taking Esmya within the first week of your menstrual period.
The tablet should be swallowed with water and may be taken with or without food.

If you take more Esmya than you should
Experience with Esmya when several doses are taken at once is limited. There have been no reports of serious harmful effects from taking several doses of this medicine at once. You should nonetheless ask your doctor or pharmacist for advice if you take more Esmya than you should.

If you forget to take Esmya
If you miss a dose by less than 12 hours, take it as soon as you remember. If you miss a dose by more than 12 hours, skip the missed tablet and take only a single tablet as usual. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Esmya
Esmya can be taken daily for up to 3 months continuously. Do not stop taking your tablets without the advice of your doctor even if you feel better, as symptoms may re-occur later.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common (may affect more than 1 in 10 people) side effects:
- reduction or absence of menstrual bleeding (amenorrhea)
- thickening of the lining of the womb (endometrial thickening).

Common (may affect up to 1 in 10 people) side effects:
- headache
- spinning sensation (vertigo)
- stomach ache, feeling sick (nausea)
- acne
- increased sweating
- muscle and bone (musculoskeletal) pain
- sac of fluid within the ovaries (ovarian cyst), breast tenderness/pain, lower abdominal (pelvic) pain, bleeding from the womb (uterine bleeding)
- hot flushes
- swelling due to fluid retention (oedema)
- tiredness (fatigue)
- increase in blood cholesterol seen in blood tests.

Uncommon (may affect up to 1 in 100 people) side effects:
- anxiety

- mood swings
- dizziness
- nosebleed
- indigestion, dry mouth, bloating, constipation
- hair loss, dry skin
- back pain
- leakage of urine
- break of sac of fluid within the ovaries (ovarian cyst)
- vaginal discharge, abnormal vaginal bleeding
- breast swelling, breast discomfort
- extreme tiredness (asthenia)
- weight increase
- increase in blood fats (triglycerides) seen in blood tests.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Esmya

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the blister after EXP. The expiry date refers to the last day of that month.

Keep the blister in the outer carton in order to protect from light.

Do not throw away via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Esmya contains
- The active substance is ulipristal acetate. One tablet contains 5 mg of ulipristal acetate.
- The other ingredients are microcrystalline cellulose, mannitol, croscarmellose sodium, talc and magnesium stearate.

What Esmya looks like and contents of the pack
Esmya is white to off-white, round curved tablet of 7 mm engraved with code “ES5” on one face.
Esmya is available in Alu-PVC/PE/PVDC blisters in cartons containing 28 and 84 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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

Manufacturer:
Cenexi
17 rue de Pontoise
F-95520 Osny
France

Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu