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 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.

4.2 Posology and method of administration

Esmya treatment is to be initiated and supervised by physicians experienced in the diagnosis and treatment of uterine fibroids.

Posology
The treatment consists of one tablet of 5 mg to be taken once daily for treatment courses of up to 3 months each. Tablets may be taken with or without food.
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 courses.

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).

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
Oral use. Tablets should be swallowed with water.

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.
Underlying hepatic disorder.

4.4 Special warnings and precautions for use

Ulipristal acetate should only be prescribed after careful diagnosis. Pregnancy should be precluded prior to treatment. If pregnancy is suspected prior to initiation of a new treatment course, a pregnancy test should be performed.

Contraception
Concomitant use of progestagen-only pills, a progestagen-releasing intrauterine device or combined oral contraceptive pills is not recommended (see section 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.

Endometrial changes
Ulipristal acetate has a specific pharmacodynamic action on the endometrium:
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).
In addition, reversible increase of the endometrium thickness may occur under treatment.

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 (see section "Bleeding pattern" below), investigation including endometrial biopsy should be performed in order 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.

The treatment courses should each not exceed 3 months as the risk of adverse impact on the endometrium is unknown if treatment is continued without interruption.

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 generally return within 4 weeks after the end of each treatment course.
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 of the endometrium including endometrial biopsy should be performed in order to exclude other underlying conditions, including endometrial malignancy.

Repeated intermittent treatment has been studied up to 4 intermittent treatment courses.

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 injury
During the post-marketing experience, cases of liver injury and hepatic failure were reported (see section 4.3).
Liver function tests must 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 treatment has stopped.

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.

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 medicinal 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).

Breastfeeding
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 breastfeeding (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 1,053 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 (79.2%), 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 (95.0%), did not lead to discontinuation of the medicinal product (98.0%) and resolved spontaneously.
Among these 1,053 women, the safety of repeated intermittent treatment courses (each limited to 3 months) has been evaluated in 551 women with uterine fibroids treated with 5 or 10 mg ulipristal acetate in two phase III studies (including 446 women exposed to four intermittent treatment courses of whom 53 were exposed to eight intermittent treatment courses) and demonstrated a similar safety profile to that observed for one treatment course.

Tabulated list of adverse reactions
Based on pooled data from four 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 during treatment course 1				
	Very common	**Common**	**Uncommon**	**Rare**	**Frequency Not known**
Immune system disorders			Drug hypersensitivity*		
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	Dry mouth Constipation	Dyspepsia Flatulence	
Hepatobiliary disorders					Hepatic failure
Skin and subcutaneous tissue disorders		Acne	Alopecia** Dry skin Hyperhidrosis		Angioedema
Musculoskeletal and connective tissue disorders		Musculoskeletal pain	Back pain		
Renal and urinary disorders			Urinary incontinence		
Reproductive system and breast disorders	Amenorrhea Endometrial thickening*	Hot flush* Pelvic pain Ovarian cyst* Breast tenderness/pain	Uterine haemorrhage* Metrorrhagia Genital discharge Breast discomfort	Ovarian cyst ruptured* Breast swelling	
General disorders and administration site conditions		Fatigue	Oedema Asthenia		
Investigations		Weight increased	Blood cholesterol increased Blood triglycerides increased		

* see section "Description of selected adverse reactions"

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

When comparing repeated treatment courses, overall adverse reactions rate was 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 for dyspepsia which was classified as uncommon in treatment course 3 based on one patient occurence).

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 by the end of the first 3-month treatment course. In subsequent treatment courses, endometrial thickening was less frequently observed (4.9% and 3.5% of patients by the end of second and fourth treatment course, respectively). The endometrial thickening 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 8.1% of 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 first 3-month treament course of the two long term Phase III trials, the frequency was 5.3% and 5.8% for ulipristal acetate, respectively.

Drug hypersensitivity
Drug hypersensitivity symptoms such as generalised oedema, pruritus, rash, swelling face or urticaria were reported by 0.4% of patients in Phase III trials.

Headache
Mild or moderate severity headache was reported in 5.8% of patients.

Ovarian cyst
Functional ovarian cysts were observed during and after treatment in 1.0% 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.

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.

Mechanism of action
Ulipristal acetate exerts a direct effect on the endometrium.

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

Pharmacodynamic effects

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 the first 3-month treatment course. In case of repeated treatment courses, endometrial thickening was less frequently observed (4.9% of patients after second treatment course and 3.5% after fourth treatment course). This thickening disappears after treatment is withdrawn and menstruation occurs. If endometrial thickness persists after return of menstruations during off-treatment periods or beyond 3 months following the end of treatment courses, it may need to be investigated as per usual clinical practice to exclude other underlying conditions.

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.

Clinical efficacy and safety

Pre-operative use:

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 medicinal product. 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.

Repeated intermittent use:
The efficacy of repeated treatment courses fixed doses of ulipristal acetate 5 mg or 10 mg once daily was evaluated in two Phase 3 studies assessing up to 4 intermittent 3-month treatment courses in patients with heavy menstrual bleeding associated with uterine fibroids. Study 3 was on open-label study assessing ulipristal acetate 10 mg, where each of the 3-month treatment was followed by 10 days of double-blind treatment with progestin or placebo. Study 4 was a randomized, double-blind clinical study assessing ulipristal acetate 5 or 10 mg.

Studies 3 and 4 showed efficacy in controlling uterine fibroid symptoms (e.g. uterine bleeding) and reducing fibroid size after 2 and 4 courses.
In study 3, treatment efficacy has been shown over > 18 months of repeated intermittent treatment (4 courses of 10 mg once daily), 89.7% of patients were in amenorrhea at the end of the treatment course 4.
In study 4, 61.9% and 72.7% of patients were in amenorrhea at the end of both treatment course 1 and 2 combined (5 mg dose and 10 mg dose, respectively, p=0.032); 48.7 % and 60.5 % were

in amenorrhea at the end of all four treatment courses combined (5 mg dose and 10 mg dose, respectively, p=0.027). At the end of treatment course 4, 158 (69.6%) subjects and 164 (74.5%) subjects were assessed as being in amenorrhea, in the 5 mg dose and 10 mg dose respectively (p=0.290).

Table 2: Results of primary and selected secondary efficacy assessments in long term Phase III studies

Parameter	**After treatment course 2** (two times 3 months of treatment)			**After treatment course 4** (four times 3 months of treatment)		
	Study 3[a]	**Study 4**		**Study 3**	**Study 4**	
Patients starting treatment course 2 or 4	**10 mg/day** N=132	**5 mg/day** N=213	**10 mg/day** N=207	**10 mg/day** N=107	**5 mg/day** N=178	**10 mg/day** N=176
Patients in **amenorrhea**[b,c]	N=131	N=205	N=197	N=107	N=227	N=220
	116 (88.5%)	152 (74.1%)	162 (82.2%)	96 (89.7%)	158 (69.6%)	164 (74.5%)
Patients with **controlled bleeding**[b,c, d]	NA	N=199	N=191	NA	N=202	N=192
		175 (87.9%)	168 (88.0%)		148 (73.3%)	144 (75.0%)
Median change in **myoma volume** from baseline	-63.2%	-54.1%	-58.0%	-72.1%	-71.8%	-72.7%

[a] Treatment course 2 assessment corresponds to Treatment course 2 plus one menstrual bleeding.

[b] Patients with missing values were exluded from the analysis.

[c] N and % include withdrawn patients

[d] Controlled bleeding was defined as no episodes of heavy bleeding and a maximum of 8 days of bleeding (not including days of spotting) during the last 2 months of a treatment course.

In all Phase III studies including repeated intermittent treatment studies, a total of 7 cases of hyperplasia were observed out of 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, including data on 340 women who received up to 4 courses of ulipristal acetate 5 or 10 mg and limited data of 43 women who received up to 8 courses of ulipristal acetate 10 mg. 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).

Paediatric population

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.h/ml and 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.h/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. Esmya is contraindicated in patients with hepatic disorder (see section 4.3 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 or Alu/PVC/PVDC blister.
Pack of 28, 30 and 84 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 February 2012
Date of latest renewal: 14 November 2016