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.
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. 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 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.

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 thichness 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 ‘bleeding pattern’), 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.

Only two treatment courses are recommended. 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 will generally return within 4 weeks after the end of the treatment course.
If, 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.

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.

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 Cmax 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 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 457 women exposed to four intermittent traetment 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**			
	Very common	**Common**	**Uncommon**	**Rare**
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
Skin and subcutaneous tissue disorders		Acne	Alopecia** Dry skin Hyperhidrosis	
Musculoskeletal and		Musculoskeletal pain	Back pain	

connective tissue disorders				
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 triglycerides increased Blood cholesterol 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.

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. 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% 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

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.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il).

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 the first 3-month treatment course. This thickening disappears after treatment is withdrawn and menstruation occurs. If endometrial thickness persists beyond the 3 months following the end of treatment courses, it 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.

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 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.

Endometrial findings:
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. 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).

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 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 (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
Talc
Croscarmellose sodium

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25 ºC.
Keep the blisters in the outer carton in order to protect from light.

6.5 Nature and contents of container

PVC-PE-PVDC-Aluminium or PVC-PVDC-Aluminium blister.
Pack of 28 or 84 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MANUFACTURER

Laboratoire HRA Pharma
15 rue Béranger
75003 Paris
France

8. LICENSE HOLDER/ IMPORTER

CTS Ltd,
4 Haharash st.
Hod - Hasharon

9. REGISTRATION AUTHORISATION NUMBER : 155-35-24283

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved by it on January 2016