ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Intrarosa 6.5 mg pessary.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pessary contains 6.5 mg of prasterone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pessary.

White to off-white, bullet-shaped pessary approximately 28 mm long and 9 mm in diameter at its widest end.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Intrarosa is indicated for the treatment of vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms.

4.2 Posology and method of administration

Posology
The recommended dose is 6.5 mg prasterone (one pessary) administered once daily, at bedtime.

For the treatment of postmenopausal symptoms, Intrarosa should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be reassessed at least every 6 months and Intrarosa should only be continued as long as the benefit outweighs the risk.

If a dose is forgotten, it should be taken as soon as the patient remembers. However, if the next dose is due in less than 8 hours, the patient should skip the missed pessary. Two pessaries should not be used to make up for a forgotten dose.

Special populations

Elderly
No dose adjustment is considered necessary in elderly women.

Patients with renal and/or hepatic impairment
Since Intrarosa acts locally in the vagina, no dosage adjustment is needed for postmenopausal women having renal or hepatic impairment or any other systemic anomaly or disease.

Paediatric population
There is no relevant use of Intrarosa in female children of any age group for the indication of vulvar and vaginal atrophy due to menopause.

Method of administration

Vaginal use.

Intrarosa can be inserted in the vagina with the finger or with an applicator provided within the identified pack.

The pessary should be inserted in the vagina as far as it can comfortably go without force.

If inserted with an applicator, the following steps should be followed:

1. The applicator should be activated (by pulling back the plunger) before use.
2. The flat end of the pessary should be placed into the open end of the activated applicator.
3. The applicator should be inserted into the vagina as far as it can comfortably go without force.
4. The plunger of the applicator should be pressed to release the pessary.
5. The applicator should then be withdrawn and disassembled, and the two pieces of the applicator should be rinsed for 30 seconds under running water before wiping with paper towel and reassembled. The applicator should be kept in a clean place until next use.
6. Each applicator should be discarded after one week of usage (two extra applicators are provided).

4.3 Contraindications

- Hypersensitivity to the active substance or to the excipient listed in section 6.1;
- Undiagnosed genital bleeding;
- Known, past or suspected breast cancer;
- Known or suspected oestrogen-dependent malignant tumours (e.g endometrial cancer);
- Untreated endometrial hyperplasia;
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal
- Previous or current venous thromboembolism (deep vein thrombosis, pulmonary embolism);
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4);
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction);
- Porphyria.

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, Intrarosa should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be reassessed at least every 6 months and Intrarosa should only be continued as long as the benefit outweighs the risk following discussions with their doctor.

Before initiating Intrarosa, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and special warnings and precautions for use according to the decision of their doctor. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see ‘Breast cancer’ below). Investigations, including Pap smears and blood pressure measurements should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision

- If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Intrarosa, in particular:
  – Leiomyoma (uterine fibroids) or endometriosis
  – Risk factors for thromboembolic disorders (see below)
  – Risk factors for oestrogen dependent tumours, e.g. 1st degree heredity for breast cancer
  – Hypertension
  – Liver disorders (e.g. liver adenoma)
  – Diabetes mellitus with or without vascular involvement
  – Cholelithiasis
  – Migraine or (severe) headache
  – Systemic lupus erythematosus.
  – A history of endometrial hyperplasia (see below)
  – Epilepsy
  – Asthma
  – Otosclerosis

Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contraindication is discovered and in the following situation:
– Jaundice or deterioration in liver function
– Significant increase in blood pressure
– New onset of migraine-type headache
– Pregnancy.

Endometrial hyperplasia and carcinoma

- Estrogen is a metabolite of prasterone. In women with an intact uterus, the risk of endometrial hyperplasia and carcinoma is increased when exogenous oestrogens are administered for prolonged periods. No cases of endometrial hyperplasia have been reported in women treated for 52 weeks during the clinical studies. Intrarosa has not been studied in women with endometrial hyperplasia.
- For oestrogen products for vaginal application of which the systemic exposure to oestrogen remains within the normal postmenopausal range, it is not recommended to add a progestagen.
- Endometrial safety of long-term of local vaginally administered prasterone has not been studied for more than one year. Therefore, if repeated, treatment should be reviewed at least annually.
- If bleeding or spotting appears at any time on therapy, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.
- Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore caution is advised when using this product in women who have undergone hysterectomy because of endometriosis, especially if they are known to have residual endometriosis since intravaginal prasterone has not been studied in women with endometriosis.

Prasterone is metabolised into estrogenic compounds. The following risks have been associated with systemic HRT and apply to a lesser extent for oestrogen products for vaginal application of which the systemic exposure to the oestrogen remains within the normal postmenopausal range. However, they should be considered in case of long term or repeated use of this product.

Breast cancer

The overall evidence suggests an increased risk of breast cancer in women taking combined oestrogen-progestagen and possibly also oestrogen-only systemic HRT, that is dependent on the duration of taking HRT. The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment.

Intrarosa has not been studied in women with active or past breast cancer. One case of breast cancer at week 52 has been reported on 1196 women who have been exposed with the 6.5 mg dose which is below the incidence rate observed in the normal population of the same age.

Ovarian cancer
Ovarian cancer is much rarer than breast cancer.
Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only systemic HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.

Intrarosa has not been studied in women with active or past ovarian cancer. One Case of ovarian cancer has been reported on 1196 women who have been exposed with the 6.5 mg dose which is above the incidence rate observed in the normal population of the same age. Of note, this case was present before start of treatment and was bearing a BRCA1 mutation.

Abnormal Pap smear
Intrarosa has not been studied in women with abnormal Pap smears (Atypical Squamous Cells of Undetermined Significance (ASCUS)) or worse. Cases of abnormal Pap smears corresponding to ASCUS or Low Grade Squamous Intraepithelial Lesion (LSIL) have been reported in women treated with the 6.5 mg dose (common frequency).

Venous thromboembolism
Intrarosa has not been studied in women with current or previous venous thromboembolic disease.

- Systemic HRT is associated with a 1.3-3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see section 4.8).
- Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).
- Generally recognised risk factors for VTE include, use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m^2), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE.
  As in all postoperative patients, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.
- In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening).
  If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g, antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.
- Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.
- If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

One case of pulmonary embolism has been reported in the 6.5 mg group and one in the placebo group during clinical trials.

Coronary artery disease (CAD)/ Hypertension
Intrarosa has not been studied in women with uncontrolled hypertension (blood pressure above 140/90 mmHg) and cardiovascular disease. Cases of hypertension have been reported in clinical trials with an uncommon frequency and similar incidence rates were observed in both groups (6.5 mg prasterone and placebo). No case of coronary artery disease has been reported during clinical trials.

Ischaemic stroke
Systemic oestrogen-only therapy is associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see section 4.8).
Intrarosa has not been studied in women with current or previous arterial thromboembolic disease. No cases of arterial thromboembolic disease have been reported during clinical trials.

Other conditions observed with HRT

- Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.
- Women with pre-existing hypertriglyceridaemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.
- Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin).
- HRT use does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65.

None of these conditions has been observed with Intrarosa during the clinical trials.
Women with vaginal infection should be treated with appropriate antimicrobial therapy before starting Intrarosa.

Due to melting of the hard fat base added to an expected increase in vaginal secretions due to treatment, vaginal discharge can occur although it does not require to stop the medication (see section 4.8).

Use of Intrarosa with condoms, diaphragms or cervical caps made of latex must be avoided since the rubber may be damaged by the preparation.

Intrarosa has not been studied in women with a current hormonal treatment: hormone replacement therapy (oestrogens alone or combined with progestogens) or androgens treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use with systemic hormone replacement therapy (oestrogen-only or oestrogen-progestagen combination or androgen treatment) or vaginal oestrogens has not been investigated and is therefore not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy
Intrarosa is not indicated in pre-menopausal women of child-bearing age, including pregnancy.

If pregnancy occurs during treatment with Intrarosa, the treatment should be withdrawn immediately. There are no data on the use of Intrarosa in pregnant women.

No studies in animals were performed with regard to the reproductive toxicity (see section 5.3). The potential risk in humans is unknown.

Breast-feeding
Intrarosa is not indicated during breast-feeding.

Fertility
Intrarosa is not indicated in fertile women.

4.7 Effects on ability to drive and use machines

Intrarosa has no influence in the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile
The most frequently observed adverse reaction was vaginal discharge. This is due to melting of the hard fat used as vehicle, added to the expected increase in vaginal secretions due to treatment. It is not required to stop Intrarosa if vaginal discharge occurs (see section 4.4).

Tabulated list of adverse reactions
The adverse reaction observed with prasterone 6.5 mg pessaries obtained from clinical studies is tabulated below.

MedDRA System Organ Class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)
General disorders and administration site conditions	Application site discharge	
Reproductive system and breast disorders	Abnormal Pap smear (mostly ASCUS or LGSIL)	Cervical/ uterine polyps Breast mass (benign)
Investigations	Weight fluctuation	

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen therapy for more than 5 years.
- Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestagen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

Million Women study– Estimated additional risk of breast cancer after 5 years' use

Age range (years)	Additional cases per 1000 never-users of HRT over a 5 year period*[1]	Risk ratio & 95%CI#	Additional cases per 1000 HRT users over 5 years (95%CI)
		Oestrogen only HRT	
50-65	9-12	1.2	1-2 (0-3)

#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use

Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

*1 *Taken from baseline incidence rates in developed countries*

US WHI studies - additional risk of breast cancer after 5 years' use

Age range (yrs)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users over 5 years (95%CI)
		CEE oestrogen-only	
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*[2]

Ovarian cancer

Use of oestrogen-only or combined oestrogen-progestagen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see section 4.4).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

Risk of venous thromboembolism

HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HT (see section 4.4). Results of the WHI studies are presented:

WHI Studies - Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users
Oral oestrogen-only*[3]			
50-59	7	1.2 (0.6 - 2.4)	1 (-3 – 10)

Risk of coronary artery disease

- The risk of coronary artery disease is slightly increased in users of combined oestrogen-progestagen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke

- The use of oestrogen-only and oestrogen + progestagen therapy is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.
- This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age, see section 4.4.

WHI studies combined - Additional risk of ischaemic stroke*[4] over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users over 5 years
50-59	8	1.3 (1.1-1.6)	3 (1-5)

Other adverse reactions have been reported in association with oestrogen/progestagen treatment:

– *Gall bladder disease.*

*2 *WHI study in women with no uterus, which did not show an increase in risk of breast cancer*

*3 *Study in women with no uterus*

4 **no differentiation was made between ischaemic and haemorrhagic stroke.*

- *Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.*
- *Probable dementia over the age of 65 (see section 4.4).*

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

In the event of overdose, vaginal douching is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other sex hormones and modulators of the genital system,
ATC code: G03XX01.

Mechanism of action
Intrarosa contains the active ingredient prasterone, i.e. dehydroepiandrosterone (DHEA), which is biochemically and biologically identical to the endogenous human DHEA, a precursor steroid which is inactive by itself and it is converted into oestrogens and androgens. Intrarosa is thus different from the oestrogens preparations since it delivers also androgen metabolites.

An oestrogen-mediated increase in the number of superficial and intermediate cells and decrease in the number of parabasal cells in the vaginal mucosa is noted. In addition, the vaginal pH decreased towards the normal range, thus facilitating the growth of the normal bacterial flora.

Clinical efficacy
Physiological responses (objective measures)
Efficacy data were obtained from two US and Canadian randomised, double-blind, placebo-controlled, multicentre, pivotal phase III trials (ERC-231/Trial 1 and ERC-238/Trial 2) performed in postmenopausal women aged 40 to 80 years (mean age = 58.6 years in Trial 1 and 59.5 years in Trial 2) with vulvar and vaginal atrophy (VVA). At baseline, women had ≤ 5.0% superficial cells in the vaginal smear, a vaginal pH > 5.0 and they had identified dyspareunia (moderate to severe) as their most bothersome symptom (MBS) of VVA. After 12 weeks of daily treatment with a prasterone 6.5 mg pessary (n=81 in Trial 1 and n=325 in Trial 2), the change from baseline, in comparison with placebo treatment (n=77 in Trial 1 and n=157 in Trial 2), demonstrated significant improvements of the 3 co-primary endpoints compared to placebo in both studies, namely increase of the percentage of superficial cells ($p<0.0001$), decrease of the percentage of parabasal cells ($p<0.0001$), and decrease in the vaginal pH ($p<0.0001$).

Symptoms (subjective measures)
The most bothersome symptom (MBS) dyspareunia (co-primary endpoint) was assessed at baseline and 12 weeks with the severity scored as follows: None=0, Mild=1, Moderate=2, Severe=3.
Table 1 shows the mean change in severity score in MBS dyspareunia after 12 weeks with associated statistical testing for the difference vs. placebo for Trial 1 (ERC-231) and Trial 2 (ERC-238).

Table 1: Primary Efficacy Analysis – Change from Baseline to Week 12 in the Most Bothersome Symptom Dyspareunia (ITT Population; LOCF)

Study	Dyspareunia		
	Intrarosa 6.5 mg	**Placebo**	**p-value**
Trial 1	-1.27	-0.87	0.0132
Trial 2	-1.42	-1.06	0.0002

Table 2 shows the percentage of subjects who reported a change from baseline in their MBS dyspareunia at week 12. "Improvement" was defined as a reduction in the severity score of 1 or more. "Relief" was defined as no or only mild symptoms at week 12. "Substantial improvement" was restricted to patients who had moderate or severe MBS at baseline and changed from severe to mild or severe or moderate to none.

Table 2: Percentage of Patients with Improvement, Relief or Substantial Improvement of MBS Dyspareunia after 12 Weeks on Intrarosa vs. Placebo (ITT, LOCF)

	Improvement		**Relief**		**Substantial improvement**	
	Intrarosa	**Placebo**	**Intrarosa**	**Placebo**	**Intrarosa**	**Placebo**
Trial 1 (Intrarosa: n= 81) (Placebo: n= 77)	72.8% (p=0.0565)	58.4%	58.0% (p=0.0813)	44.2%	43.2% (p=0.0821)	29.9%
Trial 2 (Intrarosa: n= 325) (Placebo: n= 157)	80.3% (p=0.0003)	65.0%	68.6% (p=0.0003)	51.6%	47.1% (p=0.0179)	35.7%

Clinical safety
Apart from the main two 12-week phase III clinical studies, the safety data of Intrarosa has also been obtained from one non comparative open-label safety study of one year.

Cases of breast and ovarian cancer have been reported in women treated with 6.5 mg of prasterone for 52 weeks (see section 4.4).

Cases of abnormal Pap smears either Atypical Squamous Cells of Undetermined Significance (ASCUS) or Low Grade Squamous Intraepithelial Lesion (LSIL) have been reported with a common frequency in women treated with Intrarosa for 52 weeks (see section 4.4).

Endometrial safety
On the 389 evaluable end-of-study endometrial biopsies performed after 52 weeks of treatment with Intrarosa, no histological abnormalities were reported on the biopsies.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Intrarosa in all subsets of the paediatric population.

5.2 Pharmacokinetic properties

Absorption
Prasterone administered in the vagina is an inactive precursor that enters the vaginal cells and is converted intracellularly into cell-specific small amounts of both oestrogens and androgens depending upon the level of enzymes expressed in each cell type. The beneficial effects on the symptoms and

signs of vulvar and vaginal atrophy are exerted through activation of the vaginal oestrogen and androgen receptors.
In a study conducted in postmenopausal women, administration of the Intrarosa pessary once daily for 7 days resulted in a mean prasterone C_{max} and area under the curve from 0 to 24 hours (AUC_{0-24}) at day 7 of 4.4 ng/mL and 56.2 ng h/mL, respectively, which were significantly higher than those in the group treated with placebo (Table 3; Figure 1). The C_{max} and AUC_{0-24} of the metabolites testosterone and estradiol were also slightly higher in women treated with the Intrarosa pessary compared to those receiving placebo but all remained within normal values of postmenopausal women (< 10 pg estradiol/mL; < 0.26 ng testosterone/mL) as measured by validated mass spectrometry-based assays for both the study samples and reference values.

Table 3: C_{max} and AUC_{0-24} of Prasterone, Testosterone, and Estradiol on Day 7 Following Daily Administration of Placebo or Intrarosa (mean ± S.D.)

		Placebo (N=9)	**INTRAROSA** (N=10)
Prasterone	C_{max} (ng/mL)	1.60 (±0.95)	4.42 (±1.49)
	AUC_{0-24} (ng·h/mL)	24.82 (±14.31)	56.17 (±28.27)
Testosterone	C_{max} (ng/mL)	0.12 (±0.04)[1]	0.15 (±0.05)
	AUC_{0-24} (ng·h/mL)	2.58 (±0.94)[1]	2.79 (±0.94)
Estradiol	C_{max} (pg/mL)	3.33 (±1.31)	5.04 (±2.68)
	AUC_{0-24} (pg·h/mL)	66.49 (±20.70)	96.93 (±52.06)

[1] : N=8

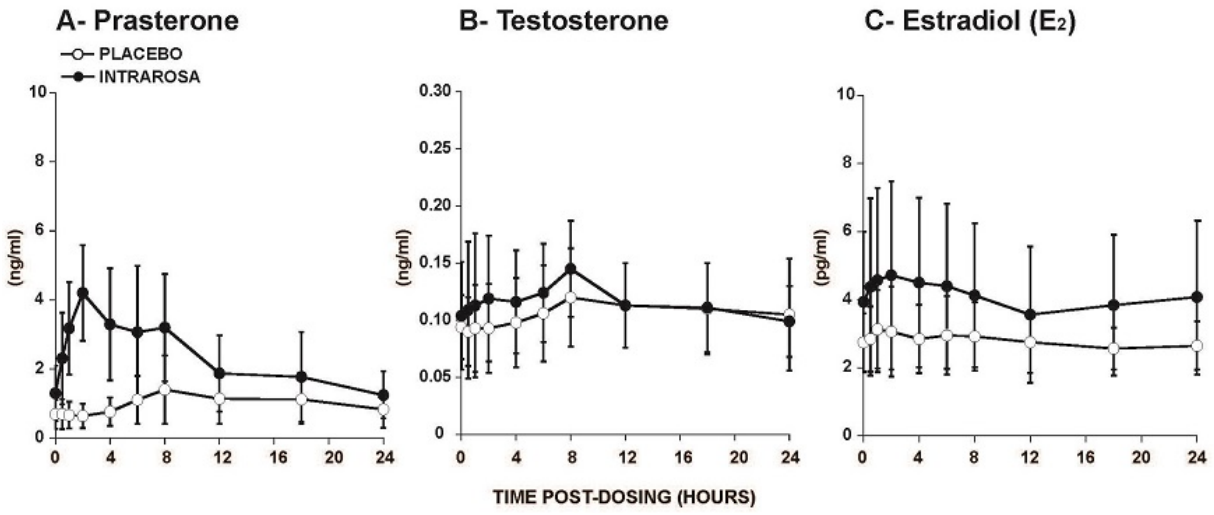

Figure 1: Serum Concentrations of Prasterone (A), Testosterone (B), and Estradiol (C) Measured Over a 24h Period on Day 7 Following Daily Administration of Placebo or Intrarosa (mean ± S.D.)

Distribution
The distribution of intravaginal (exogenous) prasterone is mainly local but some increase in systemic exposure is observed especially for the metabolites but within normal values.

Biotransformation
Exogenous prasterone is metabolized in the same manner as endogenous prasterone. Systemic metabolism has not been studied in this application.

Elimination
Systemic elimination has not been studied specifically for this application.

5.3 Preclinical safety data

Prasterone was not mutagenic or clastogenic in a standard battery of *in vitro* and in *vivo* studies.

Carcinogenic and reproductive and development toxicity studies were not performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard fat (adeps solidus).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30 °C.

Do not freeze.

6.5 Nature and contents of container

Blister composed of an outer layer of PVC and an inner layer of LDPE.

Applicator made of LDPE and 1% colorant (Titanium dioxide).

28 pessaries are packed in a carton with 6 applicators.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Endoceutics S.A.
Rue Belliard 40
1040 Brussels
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1255/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 january 2018

10. DATE OF REVISION OF THE TEXT

03/2019

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