ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 dose 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 The applicator should then be withdrawn and disassembled, and the two pieces of the applicator should be rinsed for 30 seconds under running water before wiping with paper towel and reassembled.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 (VTE) (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.

Medical examination/follow-up

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*** *Hormone Replacement Therapy (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, Intrarosa 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 studies.

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 studies 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 studies.

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 studies.

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 HRT, 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 studies.
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 Intrarosa (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: HRT (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 HRT (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

Adverse reactions observed with prasterone 6.5 mg pessaries obtained from clinical studies are tabulated in Table 1 below.

Table 1: Adverse reactions observed with prasterone 6.5 mg pessaries in clinical studies

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 study (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.

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

Age range (years)	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 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).

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

*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*

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.
- 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 substance 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.

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

Clinical efficacy

Physiological responses (objective measures)

Efficacy data were obtained from two US and Canadian randomised, double-blind, placebo-controlled, multicentre, pivotal phase III studies (ERC-231/Study 1 and ERC-238/Study 2) performed in postmenopausal women aged 40 to 80 years (mean age = 58.6 years in Study 1 and 59.5 years in Study 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 Study 1 and n=325 in Study 2), the change from baseline, in comparison with placebo treatment (n=77 in Study 1 and n=157 in Study 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 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 2 shows the mean change in severity score in MBS dyspareunia after 12 weeks with associated statistical testing for the difference vs. placebo for Study 1 (ERC-231) and Study 2 (ERC-238).

Table 2: 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**
Study 1	-1.27	-0.87	0.0132
Study 2	-1.42	-1.06	0.0002

Table 3 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 3: 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**
Study 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%
Study 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 ASCUS or 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 4; 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 4: 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

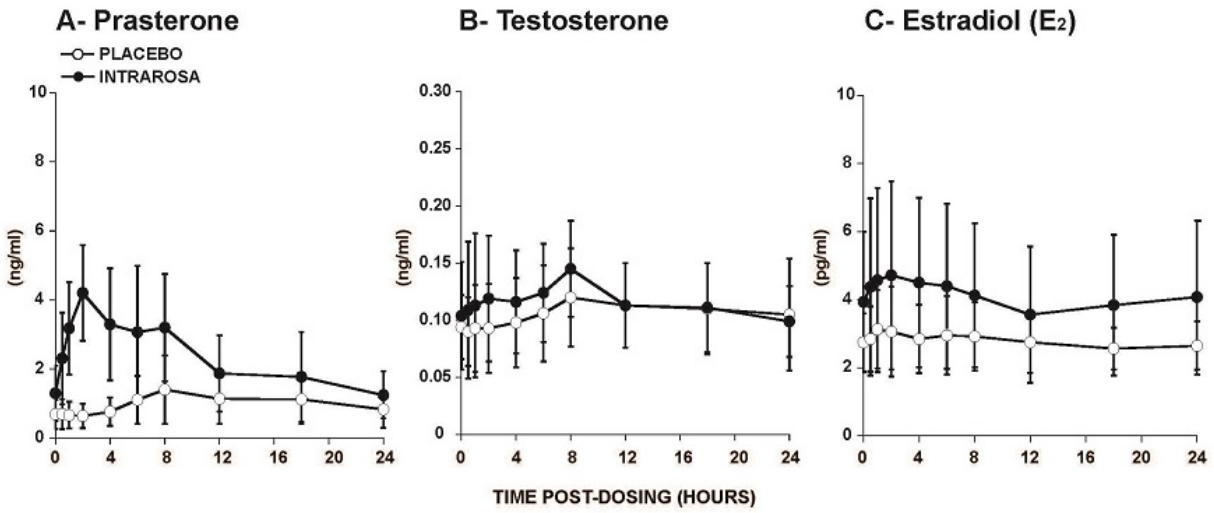

Figure 1: **Serum concentrations of prasterone (A), testosterone (B), and estradiol (C) measured over a 24h period on Day 7 following daily administration of placebo or Intrarosa (mean ± S.D.)**

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
Date of latest renewal: 15 september 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal 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. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Basic Pharma Manufacturing B.V.
Burgemeester Lemmensstraat 352
6163 JT Geleen
THE NETHERLANDS

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 (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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 marketing authorisation holder (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 the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Intrarosa 6.5 mg pessary
prasterone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pessary contains 6.5 mg of prasterone.

3. LIST OF EXCIPIENTS

Hard fat (adeps solidus)

4. PHARMACEUTICAL FORM AND CONTENTS

Pessary

28 pessaries and 6 applicators

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Vaginal 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

Store below 30 °C.

Do not freeze.

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

Endoceutics S.A.
Rue Belliard 40
1040 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1255/001

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Intrarosa

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Intrarosa 6,5 mg pessary
prasterone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Endoceutics

3. EXPIRY DATE

EXP

4. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Intrarosa 6.5 mg pessary
prasterone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pessary contains 6.5 mg of prasterone.

3. LIST OF EXCIPIENTS

Hard fat (adeps solidus)

4. PHARMACEUTICAL FORM AND CONTENTS

Pessary

28 pessaries

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Vaginal 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

Store below 30 °C.

Do not freeze.

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

Endoceutics S.A.
Rue Belliard 40
1040 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1255/001

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Intrarosa 6.5 mg pessary
prasterone

Read all of this leaflet carefully before you start using 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 Intrarosa is and what it is used for

Intrarosa contains the active substance prasterone.

What Intrarosa is used for

Intrarosa is used to treat postmenopausal women having moderate to severe symptoms of vulvar and vaginal atrophy. It is used to relieve menopausal symptoms in the vagina such as dryness or irritation. It is caused by a drop in the levels of oestrogen in your body. This happens naturally after the menopause.

How Intrarosa works

Prasterone corrects the symptoms and signs of vulvar and vaginal atrophy by replacing the oestrogens which are normally produced before menopause by the ovaries of women. It is inserted into your vagina, so the hormone is released where it is needed. This may relieve discomfort in the vagina.

2. What you need to know before you use Intrarosa

The use of Hormone Replacement Therapy (HRT) carries risks which need to be considered when deciding whether to start taking it, or whether to carry on taking it.

The experience in treating women with a premature menopause (due to ovarian failure or surgery) is limited. If you have a premature menopause the risks of using HRT may be different. Please talk to your doctor.

Before you start (or restart) HRT, your doctor will ask about your own and your family's medical history. Your doctor may decide to perform a physical examination. This may include an examination of your breasts and/or an internal examination, if necessary.

Once you have started using Intrarosa you should see your doctor for regular check-ups (at least every 6 months). At these check-ups, discuss with your doctor the benefits and risks of continuing with Intrarosa.

Go for regular breast screening, as recommended by your doctor.

Do not use Intrarosa
if any of the following applies to you. If you are not sure about any of the points below, talk to your doctor before taking Intrarosa,

- If you have or have ever had **breast cancer**, or if you are suspected of having it;
- If you have **cancer which is sensitive to oestrogens**, such as cancer of the womb lining (endometrium), or if you are suspected of having it;
- If you have any **unexplained vaginal bleeding;**
- If you have **excessive thickening of the womb lining** (endometrial hyperplasia) that is not being treated;
- If you have or have ever had a blood clot in a vein (thrombosis), such as in the legs (deep venous thrombosis) or the lungs (pulmonary embolism);
- If you have a blood clotting disorder (such as protein C, protein S, or antithrombin deficiency);
- If you have or recently have had a disease caused by blood clots in the arteries, such as a heart attack, stroke or angina;
- If you have or have ever had a **liver disease** and your liver function tests have not returned to normal;
- If you have a rare blood problem called "porphyria" which is passed down in families (inherited);
- If you are **allergic** to **prasterone** or any of the other ingredients of this medicine (listed in section 6 'Contents of the pack and other information').

If any of the above conditions appears for the first time while taking Intrarosa, stop taking it at once and consult your doctor immediately.

Warnings and precautions

When to take special care with Intrarosa
Tell your doctor if you have ever had any of the following problems, before you start the treatment, as these may return or become worse during treatment with Intrarosa. If so, you should see your doctor more often for check-ups:

- fibroids inside your womb;
- growth of womb lining outside your womb (endometriosis) or a history of excessive growth of the womb lining (endometrial hyperplasia);
- increased risk of developing blood clots (see "Blood clots in a vein (thrombosis)");
- increased risk of getting a oestrogen-sensitive cancer (such as having a mother, sister or grandmother who has had breast cancer);
- high blood pressure;
- a liver disorder, such as a benign liver tumour;
- diabetes;
- gallstones;
- migraine or (severe) headaches;
- a disease of the immune system that affects many organs of the body (systemic lupus erythematosus, SLE);
- epilepsy;
- asthma;
- a disease affecting the eardrum and hearing (otosclerosis);
- a very high level of fat in your blood (triglycerides);
- fluid retention due to cardiac or kidney problems.

Stop using Intrarosa and see a doctor immediately
If you notice any of the following conditions when taking HRT:

- any of the conditions mentioned in the 'Do not use Intrarosa' section;
- yellowing of your skin or the whites of your eyes (jaundice). These may be signs of a liver disease;
- if you become pregnant;
- a large rise in your blood pressure (symptoms may be headache, tiredness, dizziness);
- migraine-like headaches which happen for the first time;
- if you notice signs of a blood clot, such as:
  - painful swelling and redness of the legs;
  - sudden chest pain;
  - difficulty in breathing.

  For more information, see 'Blood clots in a vein (thrombosis)'

Note: Intrarosa is not a contraceptive. If it is less than 12 months since your last menstrual period or you are under 50 years old, you may still need to use additional contraception to prevent pregnancy. Speak to your doctor for advice.

HRT and cancer
Intrarosa has not been studied in women with current or history of cancers.

Excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the lining of the womb (endometrial cancer)
Taking oestrogen-only HRT tablets for a long time can increase the risk of developing cancer of the womb lining (the endometrium). Intrarosa does not stimulate the endometrium as shown by atrophy of the lining of the womb in all women treated with Intrarosa for one year during the clinical study.

It is uncertain whether a risk exists with Intrarosa used for long term (more than one year) treatments. However, Intrarosa has been shown to have very low absorption into the blood, therefore the addition of a progestagen is not necessary.

If you get bleeding or spotting, it's usually nothing to worry about, but you should make an appointment to see your doctor. It could be a sign that your endometrium has become thicker.

The following risks apply to HRT medicines which circulate in the blood. However Intrarosa is for local treatment in the vagina and the absorption into the blood is very low. It is less likely that the conditions mentioned below will get worse or come back during treatment with Intrarosa, but you should see your doctor if you are concerned.

Breast cancer
Evidence suggests that taking combined oestrogen-progestogen and possibly also oestrogen-only HRT increases the risk of breast cancer. The extra risk depends on how long you take HRT. The additional risk becomes clear within a few years. However, it returns to normal within a few years (at most 5) after stopping treatment.

Regularly check your breasts. See your doctor if you notice any changes such as:

- dimpling of the skin;
- changes in the nipple;
- any lumps you can see or feel.

Additionally, you are advised to join mammography screening programs when offered to you.

Ovarian cancer
Ovarian cancer is rare - much rarer than breast cancer. The use of oestrogen-only HRT has been associated with a slightly increased risk of ovarian cancer.

The risk of ovarian cancer varies with age. For example, 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. For women who have been taking HRT for 5 years, there will be about 3 cases per 2000 users (i.e. about 1 extra case).
Cases of ovarian and breast cancer have rarely been reported in women treated with 6.5 mg of prasterone for 52 weeks.

Effect of HRT on heart and circulation
Intrarosa has not been studied in women with history of thromboembolic diseases, uncontrolled hypertension or heart disease.

Blood clots in a vein (thrombosis)
The risk of blood clots in the veins is about 1.3 to 3-times higher in HRT users than in non-users, especially during the first year of taking it.

Blood clots can be serious, and if one travels to the lungs, it can cause chest pain, breathlessness, fainting or even death.

You are more likely to get a blood clot in your veins as you get older and if any of the following applies to you. Inform your doctor if any of these situations applies to you:

- you are unable to walk for a long time because of major surgery, injury or illness (see also section 3, If you need to have surgery);
- you are seriously overweight (BMI >30 kg/m^2);
- you have any blood clotting problem that needs long-term treatment with a medicine used to prevent blood clots;
- if any of your close relatives has ever had a blood clot in the leg, lung or another organ;
- you have systemic lupus erythematosus (SLE);
- you have cancer.

For signs of a blood clot, see "Stop using Intrarosa and see a doctor immediately".
In clinical studies, no deep vein thrombosis has been observed with intravaginal prasterone while one case of pulmonary embolism which corresponds to an incidence lower with Intrarosa than in the placebo group.

Compare
Looking at women in their 50s who are not taking HRT, on average, over a 5-year period, 4 to 7 in 1000 would be expected to get a blood clot in a vein.

Heart disease (heart attack) / Hypertension
For women taking oestrogen-only therapy there is no increased risk of developing a heart disease.

Stroke
The risk of getting stroke is about 1.5 times higher in HRT users than in non-users. The number of extra cases of stroke due to use of HRT will increase with age.
No case of stroke has been observed with Intrarosa during clinical studies.

Compare
Looking at women in their 50s who are not taking HRT, on average, 8 in 1000 would be expected to have a stroke over a 5-year period. For women in their 50s who are taking HRT, there will be 11 cases in 1000 users, over 5 years (i.e. an extra 3 cases).

Other conditions

- HRT will not prevent memory loss. There is some evidence of a higher risk of memory loss in women who start using HRT after the age of 65. Speak to your doctor for advice;
- You may have vaginal discharge due to melting of the 'hard fat base' which adds to increased vaginal secretions due to treatment. If vaginal discharge occurs, it is not required to stop Intrarosa.

- Intrarosa may weaken condoms, diaphragms and cervical caps made of latex.
- If you have a vaginal infection you will need a course of antibiotics before taking Intrarosa.

Children and adolescents
Intrarosa is only used in adult women.

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

No data on efficacy and safety are available in women currently treated with hormonal therapy such as: androgens, HRT (oestrogen alone or combined with progestogens).

The use of Intraorsa in combination with HRT (oestrogen-only or oestrogen-progestagen combination or androgen treatment) or vaginal oestrogens is not recommended.

Pregnancy, breast feeding and fertility
Pregnancy and breast feeding

Intrarosa is for use in postmenopausal women only. If you become pregnant, stop using Intrarosa and contact your doctor.

Fertility

Intrarosa is not meant for women with child-bearing potential. It is not known if this medicine affects fertility.

Driving and using machines
Intrarosa does not affect your ability to drive and use machines.

3. How to use Intrarosa

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
Your doctor will aim to prescribe the lowest dose to treat your symptom for as short as necessary. Speak to your doctor if you think this dose is too strong or not strong enough.

How much to use

Use one pessary once a day, at bedtime.

How to use

Insert the pessary into the vagina with your finger or with an applicator provided in the pack.

Read the instructions on how to use Intrarosa at the end of the leaflet carefully before using this medicine.

How long to use

After initial use, see your doctor at least every 6 months to check if you need to keep using Intrarosa.

If you use more Intrarosa than you should
Vaginal douching is recommended.

If you forget to use Intrarosa
If you forget to use a pessary, insert one as soon as you remember. However, if the next dose is due in less than 8 hours, skip the missed pessary.

Do not use two pessaries to make up for a forgotten dose.

If you need to have surgery
If you are going to have surgery, tell the surgeon that you are using Intrarosa. You may need to stop using Intrarosa about 4 to 6 weeks before the operation to reduce the risk of a blood clot (see section 2, 'Blood clots in a vein (thrombosis)'). Ask your doctor when you can start using Intrarosa again.

4. Possible side effects

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

The following diseases are reported more often in women using HRT medicines which circulate in the blood compared to women not using HRT. These risks apply less to vaginally administered oestrogen treatments:

- breast cancer;
- ovarian cancer;
- blood clots in the veins of the legs or lungs (venous thromboembolism);
- stroke;
- probable memory loss if HRT is started over the age of 65.

For more information about these side effects, see section 2.

The side effect the most frequently reported in the clinical studies was vaginal discharge. This is likely due to melting of the hard fat added to an expected increase in vaginal secretions due to treatment. Vaginal discharge does not require to stop Intrarosa.

The following side effects were also reported:

– with a common frequency (may affect up to 1 in 10 people): abnormal Pap smear (mostly ASCUS or LGSIL), weight fluctuations (either increase or decrease);
– with an uncommon frequency (may affect up to 1 in 100 people): benign cervical or uterine polyps, benign breast mass.

The following side effects have been reported with HRT containing estrogens but not with Intrarosa during clinical studies:

- gall bladder disease
- various skin disorders:
    - discoloration of the skin especially of the face or neck known as "pregnancy patches" (chloasma);
    - painful reddish skin nodules (erythema nodosum);
    - rash with target-shaped reddening or sores (erythema multiforme).

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 Intrarosa

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 blisters after EXP. The expiry date refers to the last day of that month.

Store below 30 °C.

Do not freeze.

Do not throw away any medicines 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 Intrarosa contains

- The active substance is prasterone. Each pessary contains 6.5 mg of prasterone.
- The only other ingredient is the hard fat (adeps solidus).

What Intrarosa looks like and contents of the pack

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

The applicator is made of LDPE and 1% colorant (titanium dioxide).

It is available in blister packs of 28 pessaries with 6 applicators.

Marketing Authorisation Holder

Endoceutics S.A.
Rue Belliard 40
1040 Brussels
Belgium

Manufacturer

Basic Pharma Manufacturing B.V.
Burgemeester Lemmensstraat 352
6163 JT Geleen
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien, Luxembourg/Luxemburg, Nederland
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Tél/Tel: + 32 (0) 28088080
INTRAROSA.Enquiries@theramex.com

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Theramex Ireland Limited
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INTRAROSA.Enquiries@theramex.com

This leaflet was last revised in

Other sources of information

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

Instructions on how to use Intrarosa

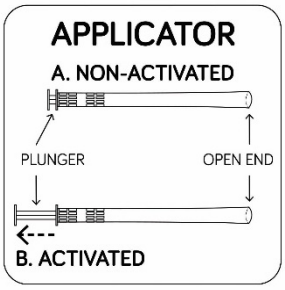
How should I use Intrarosa

- Insert one prasterone pessary in your vagina once a day at bedtime with an applicator or your finger.

Before you start

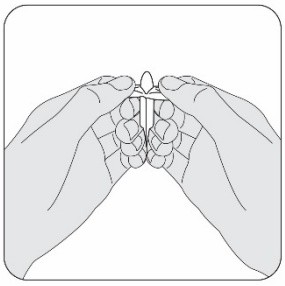
- Empty your bladder and wash your hands before handling the pessary and applicator.
- Tear off one wrapped pessary from the 7-pessary strip.

A. Using the applicator



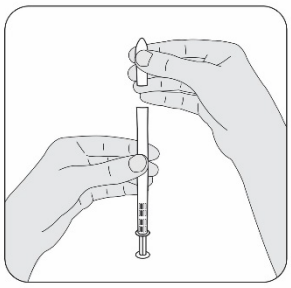
STEP 1

- 1A. Remove 1 applicator from the package.
- 1B. Pull back on the plunger until it stops to activate the applicator. The applicator must be activated before use. Place the applicator on a clean surface.



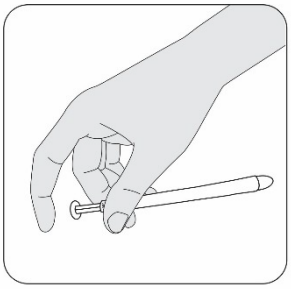
STEP 2

- Slowly pull the plastic tabs on the pessary away from each other while keeping the pessary still between your fingers.
- Carefully remove the pessary from the plastic wrap.
- If a pessary falls on an unsanitary surface, replace it with a new one.



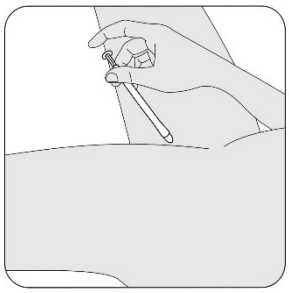
STEP 3

- Place the flat end of the pessary into the open end of the activated applicator as shown. You are now ready to insert the pessary into your vagina.



STEP 4

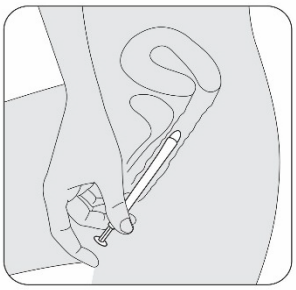
- Hold the applicator between your thumb and middle finger.
- Leave your index (pointer) finger free to press the applicator plunger after the applicator is inserted into your vagina.



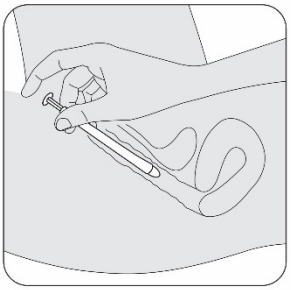
STEP 5

- Select the position for insertion of the pessary that is most comfortable for you.

5a. Lying position



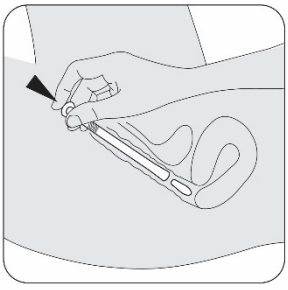
5b. Standing position



STEP 6

- Gently slide the pessary end of the applicator into your vagina as far as it will comfortably go.

Do not use force.



STEP 7

- Press the applicator plunger with your index (pointer) finger to release the pessary.
- Remove the applicator. Wash it or throw it away after using for one week (two extra applicators are provided).
- To wash the applicator:
  - Take it to pieces;
  - Rinse the 2 pieces for 30 seconds under running water;
  - Wipe with a paper towel and reassemble.

Keep it in a clean place.

B. Using the finger
Follow the above instructions of Step 2, and then insert the pessary into the vagina with your finger as far as it can comfortably go. **Do not use force.**

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report for the non-interventional imposed PASS final study report for the medicinal product(s) mentioned above, the scientific conclusions of the CHMP are as follows:

Intrarosa (prasterone) is removed from the additional monitoring list as the condition to the marketing authorisation has been fulfilled. This relates to the non-interventional PASS - Drug Utilisation Study (DUS) to describe the baseline characteristics, utilisation patterns of EU postmenopausal women initiating treatment with Intrarosa and to assess whether EU prescribers abide by the contraindications stated in the EU SmPC.

Therefore, the statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information, preceded by an inverted equilateral black triangle, is removed from the summary of product characteristics and the package leaflet.

In addition, the MAH took the opportunity to introduce a change to the list of local representatives.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for the results of the study for the medicinal product(s) mentioned above, the CHMP is of the opinion that the benefit-risk balance of these medicinal product(s) is unchanged, subject to the proposed changes to the product information.

The CHMP is of the opinion that the terms of the marketing authorisation of the medicinal product mentioned above should be varied.