▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION
INTRAROSA® prasterone 6.5 mg pessary

1 NAME OF THE MEDICINE

Prasterone

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pessary contains 6.5 mg of prasterone in hard fat.

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

INTRAROSA is a 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 Dose and method of administration

Dosage

INTRAROSA is administered intravaginally with the use of the provided applicator or with fingers.

One pessary is administered once a day 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 (or as clinically appropriate) 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 woman remembers. However, if the next dose is due in less than 8 hours, the woman should skip the missed pessary. Do not use two pessaries to make up for a forgotten dose.

Method of administration

If INTRAROSA is placed in the vagina using the provided applicator:

1. Activate the applicator (by pulling back the plunger) before use.
2. Place the flat end of the pessary into the open end of the activated applicator.

3. Insert the applicator into the vagina as far as it can comfortably go without force.
4. Press the plunger of the applicator to release the pessary.
5. Withdraw the applicator completely.
6. Disassemble the applicator and rinse the two pieces for 30 seconds under running water before drying with a paper towel or the like and then reassemble the applicator.
7. The washed applicator should be stored in a clean place, separate to the unused applicators.

Discard the applicator after one week of usage. Two extra applicators are provided.

If INTRAROSA is placed in the vagina with fingers:

1. Insert the pessary into the vagina as far as it can comfortably go without force.

4.3 Contraindications

INTRAROSA is contraindicated in women with:

- Hypersensitivity to the active substance or to the excipient listed in section 6.1 List of excipients;
- Undiagnosed genital bleeding;
- Known, past or suspected breast cancer;
- Known or suspected oestrogen-dependent malignant tumours (e.g., endometrial cancer);
- Untreated endometrial hyperplasia;
- Known or suspected pregnancy;
- 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 Special warnings and precautions for use);
- 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 (or as clinically appropriate) 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

- Oestrogen 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 progestogen.
- 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 oestrogenic 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-progestogen 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 in 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 in 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 Adverse effects (Undesirable effects)).
- 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 Contraindications).
- 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 Adverse effects (Undesirable effects)).

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 should undergo regular gynaecological and breast exams according to current Australian guidelines.

Women with vaginal infection should be treated with appropriate antimicrobial therapy before starting INTRAROSA.

Due to the 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 a stop to INTRAROSA (see section 4.8 Adverse effects (Undesirable effects)).

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.

Use in hepatic impairment

No dose adjustment is required in case of hepatic impairment. The pharmacokinetics of prasterone have not been studied in these patients.

Use in renal impairment

No dose adjustment is required in case of renal impairment. The pharmacokinetics of prasterone have not been studied in these patients.

Use in the elderly

Among 1196 patients who received INTRAROSA in clinical trials, 17% of participants in the four 12-week placebo-controlled studies were older than 65 years of age and 9.2% of participants in the 52-week open-label clinical trial were over 65 years of age. Use as recommended. No dose adjustment is required in elderly.

Paediatric use

No data available. INTRAROSA is only indicated for use in postmenopausal women.

Effects on laboratory tests

Laboratory Parameters – Hematology, serum chemistry and urinalysis parameters displayed no clinically significant changes from baseline to the final assessment (up to 12 weeks), and values generally remained within the normal adult female ranges.

Cervical Cytology – According to study protocol, participants were to have a normal Pap smear and normal mammography at study entrance. In the 521 postmenopausal women who participated in the 52-week non-comparative, open-label clinical trial, 11 cases of abnormal Pap smear (2.1%) were reported. The 11 cases of abnormal Pap smear at week 52 included 10 cases of atypical squamous cells of unknown significance (ASCUS) and 1 case of low grade squamous intraepithelial lesion (LSIL).

4.5 Interactions with other medicines and other forms of interactions

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

Interactions between INTRAROSA and other medicinal products have not been established but are not expected. Prasterone was shown not to inhibit CYP1A2, 2B7, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4 at clinically relevant concentrations *in vitro.*

Other forms of interactions

INTRAROSA can weaken condoms, diaphragms or cervical caps made of latex (see section 4.4 Special warnings and precautions for use).

INTRAROSA is not expected to interact with other substances.

4.6 Fertility, pregnancy and lactation

Effects on fertility

INTRAROSA is not indicated in fertile women. No fertility studies have been performed with prasterone in animals.

Use in pregnancy – Pregnancy Category D

INTRAROSA is contraindicated in pregnancy. There are no data on the use of INTRAROSA in pregnant women. Being only indicated in postmenopausal women, no embryofetal developmental studies have been performed with prasterone in animals. Concerns for potential adverse effects on embryofetal development are held based on the formation of oestradiol and testosterone from prasterone.

Use in lactation

INTRAROSA is not indicated during breast-feeding. There is no information on the presence of prasterone in human milk, the effects on the breastfed infant, or the effects on milk production.

4.7 Effects on ability to drive and use machines

INTRAROSA does not affect the patient's ability to drive or operate machinery.

4.8 Adverse effects (Undesirable effects)

Clinical Trial Adverse Events

The safety data for INTRAROSA was obtained from one single-centre and four multicentre, randomized, double blind, placebo-controlled PK/efficacy studies and one uncontrolled, 52 week open-label safety study. The safety data presented in Table 1 was pooled for a total of 1196 postmenopausal women treated with vaginal pessaries containing 6.5 mg of prasterone (INTRAROSA), including 435 women treated daily for one year and 474 women who received placebo.

Table 1: Treatment-Emergent Adverse Events by Primary System Organ Class and Preferred Term with an Incidence Exceeding Placebo Reported by ≥ 2% of Patients in Clinical Studies for INTRAROSA

Primary System Organ Class ***Preferred Term***	**Placebo** **n = 474** **n (%)**	**INTRAROSA** **n = 1196** **n (%)**
General disorders and administration site complications		
Application site discharge	16 (3.4)	99 (8.3)
Infections and infestations		
Urinary tract infection	21 (4.4)	57 (4.8)

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 Special warnings and precautions for use).

Tabulated list of adverse reactions

Adverse reactions observed with prasterone 6.5 mg pessaries (INTRAROSA) obtained from clinical studies are tabulated in Table 2 below.

Table 2: Adverse Reactions Observed with Prasterone 6.5 mg Pessaries (INTRAROSA) 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 LSIL)[1]	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-progestogen 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-progestogen combinations.
- The level of risk is dependent on the duration of use (see section 4.4 Special warnings and precautions for use).
- Results of the largest randomised placebo-controlled study (WHI-study) and largest epidemiological study (MWS) are presented.

Million Women study– <u>Estimated</u> 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[2]	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.

[1] *ASCUS (Atypical Squamous Cells of Undetermined Significance (ASCUS); LSIL (Low Grade Squamous Intraepithelial Lesion)*

[2] *Taken from baseline incidence rates in developed countries*

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)[3]

Ovarian cancer

Use of oestrogen-only or combined oestrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see section 4.4 Special warnings and precautions for use).

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 Special warnings and precautions for use). 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[4]			
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-progestogen HRT over the age of 60 (see section 4.4 Special warnings and precautions for use).

[3] *WHI study in women with no uterus, which did not show an increase in risk of breast cancer*
[4] *Study in women with no uterus*

Risk of ischaemic stroke

- The use of oestrogen-only and oestrogen + progestogen 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 Special warnings and precautions for use.

WHI studies combined - Additional risk of ischaemic stroke[5] 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/progestogen 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 Special warnings and precautions for use).

Reporting suspected adverse events

Reporting suspected adverse reactions after registration 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 at https://www.tga.gov.au/reporting-problems.

4.9 Overdose

No experience of overdosage is available. In the event of overdose, vaginal douching is recommended.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other sex hormones and modulators of the genital system.

ATC code: G03XX01

[5] *No differentiation was made between ischaemic and haemorrhagic stroke*

Mechanism of action

Prasterone is biochemically and biologically identical to endogenous human dehydroepiandrosterone (DHEA), a precursor steroid with no or little pharmacological activity itself that is converted into oestrogens and androgens. These metabolites formed from prasterone activate oestrogen and androgen receptors. INTRAROSA is thus different from the oestrogens preparations since it also delivers androgen metabolites.

An 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 response (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 3 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 3: 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 4 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 4: 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 Special warnings and precautions for use).

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 Special warnings and precautions for use).

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.

5.2 Pharmacokinetic properties

Absorption

Prasterone administered locally in the vagina enters the vaginal cells and is converted intracellularly into oestrogens and androgens, depending upon the level of particular steroidogenic enzymes expressed in each cell type.

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 5; Figure 1). The C_{max} and AUC_{0-24} of the metabolites testosterone and oestradiol 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 oestradiol/mL; < 0.26 ng testosterone/mL) as measured by validated mass spectrometry-based assays for both the study samples and reference values.

Table 5: C_{max} and AUC_{0-24} of Prasterone, Testosterone and Oestradiol 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)
Oestradiol	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

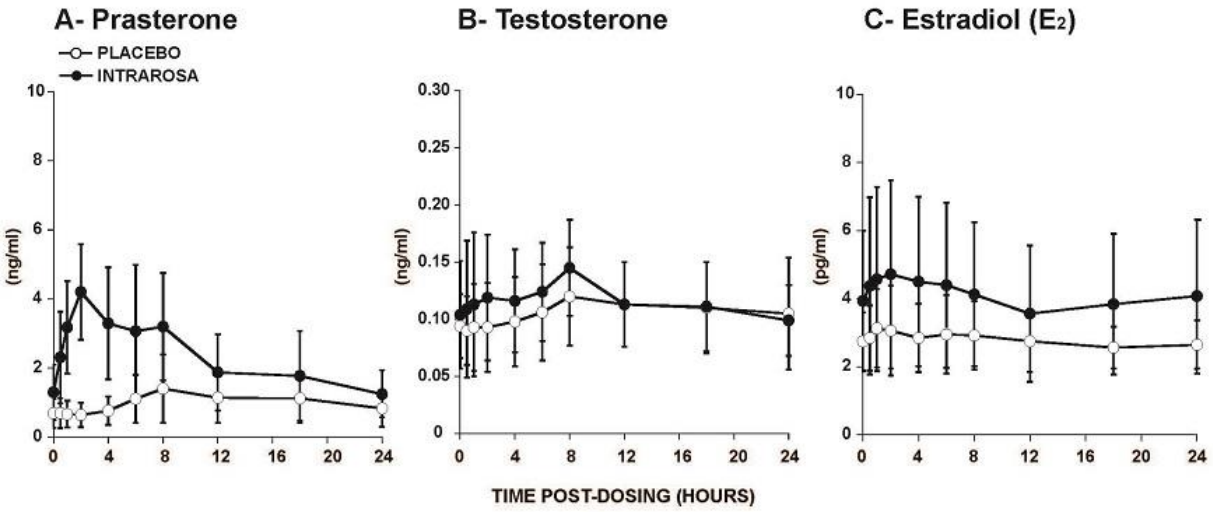


Figure 1: Serum Concentrations of Prasterone (A), Testosterone (B) and Oestradiol (C) Measured Over a 24h Period on Day 7 Following Daily Administration of Placebo or INTRAROSA (mean ± S.D.)

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.

Metabolism

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

Excretion

Systemic excretion has not been studied specifically for this application.

5.3 Preclinical safety data

Genotoxicity

Prasterone was not genotoxic in an *in vitro* bacterial mutagenicity assay (Ames test), an *in vitro* chromosomal aberration assay (performed in human lymphocytes) or *in vitro* in the mouse bone marrow micronucleus test.

Carcinogenicity

Long-term studies in animals to determine carcinogenic potential have not been performed with prasterone. Oestradiol and testosterone, two metabolites of prasterone, are carcinogenic in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard Fat

6.2 Incompatibilities

Due to the local action of INTRAROSA in the vagina, incompatibilities are not expected, see Section 4.5 Interactions with other medicines and other forms of interactions.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C. Store in original container. Do not freeze. Protect from light.

6.5 Nature and contents of container

INTRAROSA is available in a small carton box containing 4 PVC/LDPE blister packs of 7 pessaries each (28 pessaries per box). The box containing the pessaries is packed inside a larger carton box with 6 plastic applicators and the patient medication information.

INTRAROSA is available as a starter pack containing 7 pessaries with 1 plastic applicator and the patient medication information.

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

6.6 Special precautions for disposal

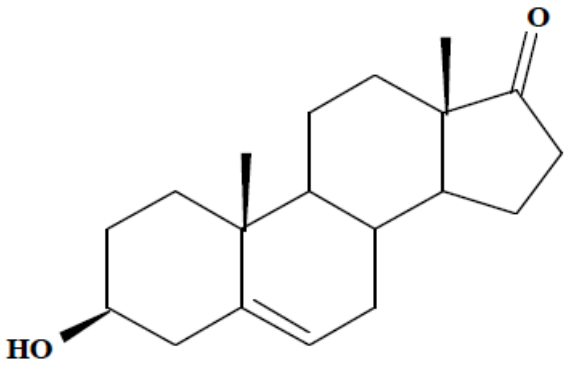
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical name: 3β-hydroxyandrost-5-en-17-one, 5-androstene-3β -ol-17-one

Molecular formula and molecular mass: $C_{19}H_{28}O_2$ (288.43 g/mol)

Chemical Structure



CAS number

53-43-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

Theramex Australia Pty Ltd
Level 22, 60 Margaret Street,
Sydney NSW 2000

1800 THERAMEX or 1800 843 726

9 DATE OF FIRST APPROVAL

16 JUNE 2023

10 DATE OF REVISION

20 SEPTEMBER 2023

10.1 Summary table of changes

Section Changed	Summary of new information
6.5	Addition of starter pack