PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

INTRAROSA®

Prasterone vaginal ovules

Ovules, 6.5 mg prasterone, vaginal

Prescribed

Treatment of postmenopausal vulvovaginal atrophy

Manufacturer/DIN Holder:
Endoceutics, Inc.
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Date of Initial Authorization:
OCT 30, 2019

Date of Revision:
OCT 20, 2021

Distributor:
Lupin Pharma Canada Limited
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Montreal, Quebec
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Submission Control No: 253873

RECENT MAJOR LABEL CHANGES

Not Applicable.

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Intrarosa® (prasterone vaginal ovules) is indicated for:

- Treatment of postmenopausal vulvovaginal atrophy.

1.1 Pediatrics

Pediatrics (< 16 years of age): Intrarosa® is indicated only for postmenopausal women.

1.2 Geriatrics

Geriatrics (> 65 years of age): Use as recommended.

2 CONTRAINDICATIONS

- Intrarosa® is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Intrarosa® is contraindicated in women with undiagnosed abnormal genital bleeding. Any postmenopausal woman with undiagnosed, persistent, or recurring genital bleeding should be adequately evaluated to determine the cause before considering initiating treatment with Intrarosa®.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

No dose adjustment is required in these situations:

- elderly women (> 65 years of age).
- in case of hepatic or renal impairment. The pharmacokinetics of prasterone have not been studied in these patients.

4.2 Recommended Dose and Dosage Adjustment

- Intrarosa® is administered intravaginally with the use of the provided applicator or with fingers.
- One vaginal ovule is administered once a day at bedtime.
- Once treatment has been initiated, women should be re-evaluated periodically, preferably every 6 months or as clinically appropriate, to determine if treatment is still necessary.
- Intrarosa® is not indicated for pediatric use.

4.4 Administration

Intrarosa® can be placed into the vagina with the use of the provided applicator:

1. Using an applicator, administer one vaginal ovule once a day at bedtime.
2. Place the vaginal ovule into the vagina as far as it can comfortably go without force.
3. Press the plunger to release the ovule.
4. Withdraw the applicator, disassemble, and rinse the two pieces for 30 seconds under running water before wiping with a paper towel or the like and reassemble.
5. Discard the applicator after one week of usage.
6. Two extra applicators are provided, if necessary.

Intrarosa® can be placed into the vagina with fingers:

1. The vaginal ovule should be placed into the vagina as far as it can comfortably go without force.

4.5 Missed Dose

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 vaginal ovule. Do not use two vaginal ovules to make up for a forgotten dose.

5 OVERDOSAGE

No experience of overdosage is available.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Vaginal	Ovule / 6.5 mg prasterone	Hard fat

Intrarosa® is a white, bullet-shaped vaginal ovule approximately 28 mm long and 8.6 mm in diameter at its widest end.

Each vaginal ovule contains 6.5 mg of prasterone in a hard fat. Intrarosa® is available in a small carton box containing 4 blister packs of 7 ovules each (28 vaginal ovules per box). The box containing the vaginal ovules is packed inside a larger carton box with 6 plastic applicators and the patient medication information.

7 WARNINGS AND PRECAUTIONS

General

Estrogen is a metabolite of prasterone. Use of exogenous estrogen is contraindicated in women with a known history of breast cancer. Intrarosa® has not been studied in women with a history of breast cancer.

- Women should undergo regular gynecological and breast exams according to current Canadian guidelines.
- Women with vaginal infection should be treated with appropriate antimicrobial therapy before starting treatment with Intrarosa®.
- The melting of the hard fat, associated with increased vaginal secretions, may result in vaginal discharge.

7.1 Special Populations

7.1.1 Pregnant Women

Intrarosa® is only indicated in postmenopausal women. There are no data on the use of Intrarosa® in pregnant women. No studies in animals were performed with regard to reproductive toxicity.

7.1.2 Breast-feeding

Intrarosa® is not indicated during breast-feeding.

It is unknown if the drug is excreted in human milk.

7.1.3 Pediatrics

Pediatrics (< 16 years of age): Intrarosa® is indicated only in postmenopausal women, therefore safety and effectiveness have not been examined in pediatric patients.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): 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 age 65. Use as recommended.

8 ADVERSE REACTIONS

8.1 Adverse Drug Reactions Overview

The adverse reactions associated with Intrarosa® were generally similar between placebo and the 6.5 mg prasterone group, except for application site discharge (3.4% for placebo versus 8.3% for 6.5 mg prasterone).

8.2 Clinical Trial Adverse Drug Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety data for Intrarosa® were obtained from one single-center and four multicenter, randomized, double blind, placebo-controlled PK/efficacy studies and one uncontrolled, 52-week open-label safety study. The safety data was pooled for a total of 1196 postmenopausal women treated with vaginal ovules containing 6.5 mg of prasterone, including 435 women treated daily for one year.

The most frequent adverse reaction (≥ 1%) reported with 6.5 mg prasterone vaginal ovules from the clinical studies was application site discharge, with an incidence of 8.3% compared to 3.4% for placebo.

Table 2 –Most Frequent Adverse Reaction (≥ 1%) Reported with Intrarosa® from Clinical Trials

System Organ Class Preferred Term	Intrarosa® n = 1196 (%)	Placebo n = 474 (%)
General Disorders and Administration Site Conditions		
Application Site Discharge	8.3	3.4

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

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.

Serum Prasterone and Related Steroid Levels - Following intravaginal administration of prasterone, serum steroid levels did not increase beyond the normal upper limits for postmenopausal women.

Endometrial Biopsies - A total of 882 women had an end-of-study endometrial biopsy in clinical trials ERC-210 (12 weeks), ERC-230 (52 weeks), ERC-231 (12 weeks) and ERC-234 (12 weeks; reduced dosing regimen). The endometrium was atrophic in 92.6% (817) of subjects.

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).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Interference of Intrarosa® with the action of other medicines is not expected.

9.3 Drug-Behavioural Interactions

Intrarosa® can weaken condoms, diaphragms or cervical caps made of latex.

Intrarosa® has no potential interaction with alcohol.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established but are not expected.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established but are not expected.

9.7 Drug-Laboratory Interactions

Interactions with laboratory tests are not expected.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Prasterone is a natural steroid compound, inactive by itself, with no estrogenic, androgenic, or other hormonal activity. Following intravaginal administration, it is transformed inside the vaginal cells into estrogens and androgens, and the sex steroids made intracellularly are also inactivated locally inside the same cells, thus avoiding exposure of other tissues. This mechanism is comparable to the physiological functioning observed in normal postmenopausal women, where the peripheral tissues make and inactivate their own intracellular sex steroids exclusively from circulating endogenous prasterone, explaining why serum estrogens and androgens remain at low concentrations following menopause and during intravaginal administration of Intrarosa®.

10.2 Pharmacodynamics

Statistically significant beneficial effects (p=0.017 to < 0.0001) were observed at 2 weeks on pH as well as on parabasal and superficial cells, with 52% to 81% of the 12-week effects observed by 2 weeks. For the effect on pain with sexual activity and vaginal dryness, the severity score decreased by 40% and 65% at 2 weeks compared to 12 weeks, an effect which became statistically significant at 8 weeks (p=0.04 and 0.004, respectively).

10.3 Pharmacokinetics

Absorption

Prasterone administered locally in the vagina is an inactive precursor of sex steroids that enters the vaginal cells and is converted intracellularly into estrogens and androgens, depending upon the level of enzymes expressed in each cell type, thus exerting beneficial effects on the symptoms and signs of vulvovaginal atrophy through activation of the vaginal estrogen and androgen receptors. Outside the vaginal cells, there are limited increases in serum estrogen (estradiol, E_2) or androgen (testosterone) concentrations, which all remain within normal postmenopausal values.

Distribution

The distribution of intravaginally administered prasterone is essentially limited to the vagina.

Metabolism

Exogenous prasterone is metabolized in the same manner as endogenous prasterone.

Elimination

Prasterone as well as the resulting estrogens and androgens formed in the vagina are inactivated intracellularly and are excreted by the kidney and liver as inactive glucuronide and sulfate conjugates.

11 STORAGE, STABILITY, AND DISPOSAL

Store between 2°C to 30°C in original package to protect from light.

Keep in safe place out of the reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

None required.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

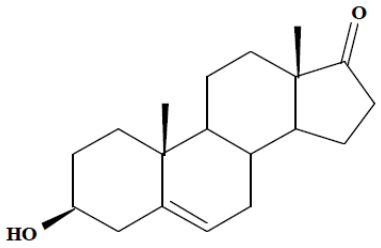
Drug Substance

Proper/Common Name: Prasterone

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)

Structural formula:



Physicochemical properties: Prasterone is a white to off-white crystalline powder.

- Prasterone occurs mainly as dimorphous needles with a melting point of 140-141°C and leaflets with a melting point of 152-153°C. Other polymorphic forms (form III, form IV, form V) and hydrates (S1, S2 and S3) are also known.
- pH: Not applicable: Prasterone is insoluble in water and possesses only an aliphatic alcohol function.
- pKa (s): Not applicable: Prasterone is insoluble in water and possesses only an aliphatic alcohol function.
- A typical DSC curve has a melting peak onset at 146.13°C with a maximum at 148.38°C (scanning at 1°C/min).
- Rotation [α] D^{25} = +11.0 to 13.0° (in ethanol 95%), as per current United States Pharmacopoeia, section <781S>.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 3 - Summary of Patient Demographics for Clinical Trials on Vulvovaginal Atrophy

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
ERC-231	Randomized (1:1:1) Double-blind Placebo-controlled	0, 3.25, or 6.5 mg Vaginal 12 weeks	255	58.6 (40 to 75)	F
ERC-238	Randomized (1:2) Double-blind Placebo-controlled	0 or 6.5 mg Vaginal 12 weeks	558	59.5 (40 to 80)	F

The effectiveness of Intrarosa® on moderate to severe dyspareunia and vaginal dryness, two symptoms of vulvovaginal atrophy due to menopause, was confirmed in two pivotal 12-week placebo-controlled efficacy trials, namely ERC-231 and ERC-238.

The first clinical trial ERC-231 was a 12-week randomized, double-blind and placebo-controlled Phase III study that enrolled 255 generally healthy postmenopausal women between 40 to 75 years of age (mean 58.6 years) who, at baseline, had identified moderate to severe dyspareunia as their most bothersome symptom of vulvovaginal atrophy. In addition to dyspareunia, women had ≤ 5% superficial cells on vaginal smear and a vaginal pH > 5. Women were randomized in a 1:1:1 ratio between the three treatment groups who received daily one vaginal ovule containing 3.25 mg prasterone (n=87), 6.5 mg prasterone (n=87) or placebo (n=81). All women were assessed for improvement in the change from baseline to week 12 for the co-primary efficacy endpoints, namely the most bothersome symptom dyspareunia, the percentage of vaginal superficial cells, the percentage of parabasal cells, and vaginal pH.

The second clinical trial ERC-238 was a 12-week randomized, double-blind and placebo-controlled Phase III study that enrolled 558 generally healthy postmenopausal women between 40 to 80 years of age (mean 59.5 years) who, at baseline, had identified moderate to severe dyspareunia as their most bothersome symptom of vulvovaginal atrophy. In addition to dyspareunia, the women had ≤ 5% superficial cells on vaginal smear and a vaginal pH > 5. Women were randomized in a 2:1 ratio between 6.5 mg prasterone (n=376) and placebo (n=182). Primary endpoints and study conduct were similar to those in Study ERC-231.

14.2 Study Results

Table 4 - Results of Study ERC-231 on Vulvovaginal Atrophy (ITT Population)

Primary Endpoints	Difference compared to placebo	P value (compared to placebo)
Dyspareunia[1,2]	- 0.40	0.0132
Superficial cells	+ 4.7 %	< 0.0001
Parabasal cells	- 45.8 %	< 0.0001
Vaginal pH	- 0.83	< 0.0001

[1] Moderate to severe dyspareunia at baseline was considered by women as their most bothersome symptom.
[2] A similar significant improvement of moderate to severe vaginal dryness was also demonstrated in this pivotal trial with p value versus placebo of 0.013.

Table 5 - Results of Study ERC-238 on Vulvovaginal Atrophy (ITT Population)

Primary Endpoints	Difference compared to placebo	P value (compared to placebo)
Dyspareunia[1,2]	- 0.35	0.0002
Superficial cells	+ 8.5 %	< 0.0001
Parabasal cells	- 29.5 %	< 0.0001
Vaginal pH	- 0.67	< 0.0001

[1] Moderate to severe dyspareunia at baseline was considered by women as their most bothersome symptom.
[2] A similar significant improvement of moderate to severe vaginal dryness was also demonstrated in this pivotal trial with p value versus placebo of 0.004.

Comparable effectiveness was observed in all four co-primary endpoints of the two pivotal 12-week clinical trials. When the severity score of moderate to severe dyspareunia considered by women at baseline as their most bothersome symptom was analyzed in the intent-to-treat (ITT) population, decreases of 0.40 and 0.35 score units compared to placebo were observed, with p values versus placebo of 0.0132 (ERC-231) and 0.0002 (ERC-238). Compared to placebo, superficial cells increased by 4.7% and 8.5%, and parabasal cells decreased by 45.8% and 29.5%, respectively, while vaginal pH decreased by 0.83 and 0.67 unit over placebo, respectively ($p< 0.0001$ versus placebo for the three parameters in both studies). A similar significant improvement of moderate to severe vaginal dryness was also demonstrated in these two pivotal trials, with p values versus placebo of 0.013 (ERC-231) and 0.004 (ERC-238).

Serum prasterone and related steroid levels were determined for women aged 40-80 years with moderate to severe symptoms of vulvovaginal atrophy (VVA) who received daily intravaginal administration of 6.5 mg prasterone for 12 weeks (n=723) compared with those who received placebo (n=266). Serum steroid levels were measured at Day 1 and week 12 by liquid chromatography-tandem mass spectrometry (LC-MS/MS). All serum sex steroid levels remained within normal postmenopausal values.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

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

Genotoxicity: The mutagenic potential of prasterone was evaluated in three standard genotoxicity assays performed under GLP conditions, namely a bacterial mutagenicity assay, a human blood lymphocyte assay, and an in vivo mouse bone marrow micronucleus assay. Prasterone was considered negative in the three genotoxicity assays.

Reproductive and Developmental Toxicology: Reproductive and teratology studies were not performed since intravaginal prasterone is for exclusive use in postmenopausal women for the proposed indication namely, vulvovaginal atrophy.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

INTRAROSA®

Prasterone Vaginal Ovules

Read this carefully before you start taking **Intrarosa®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Intrarosa®**.

What is Intrarosa® used for?

- Intrarosa® is used to treat postmenopausal women with vulvovaginal atrophy.
- At menopause, there can be a lack of sex hormones. This may cause the tissues of the vulva and vagina to become thin and dry. Below are the possible symptoms:
    - vaginal dryness.
    - pain during sexual activity.
    - irritation.
    - itching.

How does Intrarosa® work?

Prasterone is used to make sex hormones in the vagina. After menopause, prasterone is the main source of sex hormones. This medicine replaces the natural sex hormones that are missing in some women. It may improve the symptoms of vulvovaginal atrophy.

What are the ingredients in Intrarosa®?

Medicinal ingredients: Prasterone

Non-medicinal ingredients: Hard fat

Intrarosa® comes in the following dosage forms:

Vaginal ovule 6.5 mg

Intrarosa® comes in blister packs of 28. There are 6 reusable applicators in the pack. You can reuse each applicator for up to one week (two extra applicators are provided in case you need them).

Do not use Intrarosa® if:

- You have an allergy to any of the ingredients of this drug or the container.
- You have vaginal bleeding that has not been diagnosed.
- You still have periods. This drug is for postmenopausal women only.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Intrarosa®. Talk about any health conditions or problems you may have, including if you:

- have a vaginal infection. The infection will need to be treated with antibiotics before starting treatment with Intrarosa®.
- have abnormal vaginal discharge.
- have a history of breast cancer.
- can get pregnant.
- are breast-feeding.

Other warnings you should know about:

- Go for regular Pap tests, gynecological and breast exams. Do this as per your healthcare professional's directions.
- If you get pregnant, stop taking Intrarosa®. Talk with your healthcare professional.
- You must call your healthcare professional if you have vaginal bleeding while on Intrarosa®.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Intrarosa®:

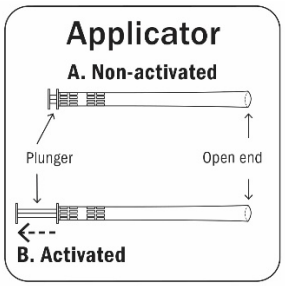
- Interactions with other drugs have not been established.

Intrarosa® can weaken condoms, diaphragms or cervical caps. This occurs if they are made of latex.

How to take Intrarosa®:

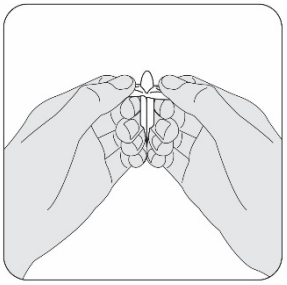
- Intrarosa® is a vaginal ovule. You place it in your vagina with the provided applicator (A), or with your fingers (B). Do not use any other applicator.
- Empty your bladder and wash your hands before handling the vaginal ovule and the applicator.
- Tear off 1 vaginal ovule along the perforations from the ovule strip.

A. Using the applicator



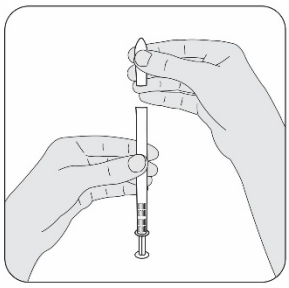
Step 1

- Remove 1 applicator from the pack. It must be activated before use.
- To activate it pull back on the plunger until it stops.
- Place the applicator on a clean surface.



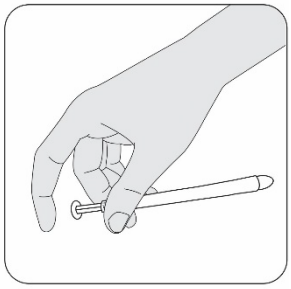
Step 2

- Keep the vaginal ovule between your fingers and slowly pull apart the plastic tabs.
- Carefully remove the ovule from the plastic wrap.
- If it falls on an unsanitary surface, replace it with a new one.



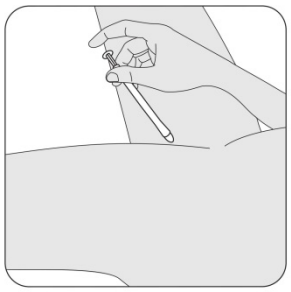
Step 3

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



Step 4

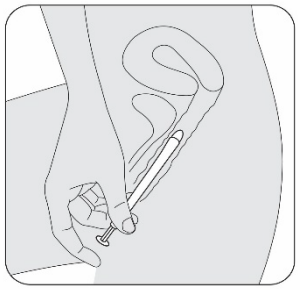
- Hold the applicator between your thumb and middle finger.
- Leave your index (pointer) finger free. You will use it to press the plunger after the applicator is placed into your vagina.



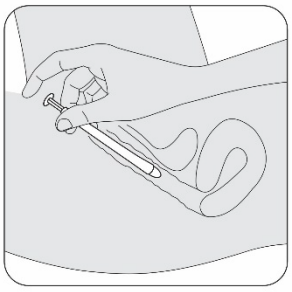
Step 5

- To place the ovule, select the position that is most comfortable for you.

5a. Lying position



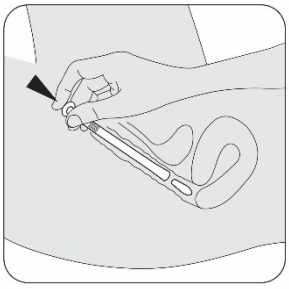
5b. Standing position



Step 6

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

Do NOT use force.



Step 7

- Press the applicator plunger with your index (pointer) finger. This will release the ovule into your vagina.
- Remove the applicator.
- Wash the applicator:
  a. take the plunger out of the body of the applicator;
  b. rinse the 2 pieces for 30 seconds under running water;
  c. wipe with a paper towel or something similar;
  d. put the applicator back together.
- Throw the applicator away after using it for one week.

B. Using fingers

Unwrap the ovule as shown above in Step 2. Place the ovule into your vagina with your fingers as far as it can comfortably go. **Do NOT use force.**

Usual Dose:

One vaginal ovule once a day at bedtime.

Dosage Adjustment:

See your healthcare professional every 6 months – or more often, if needed.

Follow your healthcare professional's recommendations.

Your healthcare professional will see if you need to keep using Intrarosa®.

Overdose:

If you think you, or a person you are caring for, have taken too much Intrarosa®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

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

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

What are possible side effects from using Intrarosa®?

These are not all the possible side effects you may have when taking Intrarosa®. If you experience any side effects not listed here, tell your healthcare professional.

The most common side effect is vaginal discharge. The leakage can be due to:

- the melting of the hard fat ingredient.
- the increased vaginal secretions.

A change in your breast exam or Pap test results can occur while you take Intrarosa®. Your healthcare professional will decide when to perform breast exams and Pap tests and will interpret the results.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax;

or

- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 2°C to 30°C in original package to protect from light.

Keep out of the reach and sight of children.

If you want more information about Intrarosa®:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html), the manufacturer's website (www.intrarosa.ca), or by calling 1-844-587-4623.

This leaflet was prepared by Endoceutics, Inc.

Last Revised OCT 20, 2021