Patient package insert according to Pharmacists' Regulations (Preparations) – 1986

This medicine can be sold with a physician's prescription only

Intrarosa®, Vaginal Pessaries, 6.5 mg

Each vaginal pessary contains prasterone 6.5 mg

Inactive ingredients and allergens in the medicine - see section 6 "Additional information".

Read this entire leaflet carefully before using this medicine. This leaflet contains concise information about the medicine. If you have any further questions, ask the doctor or pharmacist.
This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if you think that their medical condition is the same as yours.

1. What is the medicine intended for?

Intrarosa is used to treat vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms.

Therapeutic group: other sex hormones and modulators of the genital system.

How **Intrarosa** works

Intrarosa is used to relieve menopausal symptoms in the vagina such as dryness or irritation. These are caused by a drop in the levels of estrogen in your body. This happens naturally after the menopause.
Prasterone improves the symptoms and signs of vulvar and vaginal atrophy by replacing the estrogens which are normally produced before menopause by the ovaries in women. The product is inserted into your vagina, so the hormone is released where it is needed. This may relieve discomfort in the vagina.

2. Before using the medicine

The use of hormone replacement therapy (HRT) carries risks to be considered when deciding whether to start or continue treatment.

The experience in treating women who have reached menopause earlier than usual (due to ovarian failure or surgery) is limited. If you experience early menopause, the risks of alternative hormonal therapy may be different. Please consult your doctor.

Before you start using (or resume use of) hormone replacement therapy, your doctor will ask you about your medical history and that of your family. Your doctor may decide to perform a physical examination. This may include a breast examination and/or internal examination, if necessary.

Once you start using **Intrarosa**, you should have routine examinations by your doctor (at least every 6 months). During these examinations, speak with your doctor about the benefits and risks of continuing to use **Intrarosa**.

Routine breast examinations should be performed, as recommended by your doctor.

Do not use the medicine if:

One of the following applies to you. If you are not sure about any of the points below, consult your doctor before using **Intrarosa**.

- You suffer, or have ever suffered from **breast cancer**, or if you are suspected of having it;
- You suffer from a **cancer which is sensitive to estrogens**, such as cancer of the womb lining (endometrium), or if you are suspected of having it;
- You suffer from **unexplained vaginal bleeding**;
- You suffer from **excessive thickening of the** womb lining (endometrial hyperplasia) that is not being treated;
- You suffer, or have ever suffered from a blood clot in a vein (thrombosis), e.g., in the legs (deep vein thrombosis) or the lungs (pulmonary embolism);
- You suffer from a blood clotting disorder (such as protein C, protein S, or antithrombin deficiency);
- You suffer or have recently suffered from a disease caused by arterial blood clots, such as heart attack, stroke or chest pain (angina pectoris);
- You suffer, or have ever suffered from **liver disease** and your liver function tests have not returned to normal;
- You have a rare blood problem called porphyria, which is hereditary;
- You are hypersensitive (allergic) to the active ingredient (prasterone), or to any of the other ingredients this medicine contains (see section 6).

If any of the above conditions occur for the first time while using **Intrarosa**, stop using the medicine and refer to your doctor immediately.

Special warnings regarding the use of the medicine

Before the treatment with Intrarosa, tell the doctor if you have ever had one of the following problems, as they may recur or worsen during the course of treatment with **Intrarosa**. If so, you should be checked by your doctor more frequently:
- Fibroids in the uterus;
- Growth of womb lining outside your womb (endometriosis) or a history of thickening of the womb lining;
- Increased risk of developing blood clots (see "Blood clots in the vein (thrombosis)");
- Increased risk of developing estrogen-sensitive cancers (e.g., a mother, sister or grandmother who had breast cancer);
- Hypertension;
- Liver disorder, such as a benign liver tumor;
- Diabetes;
- Gallstones;
- Migraine or severe headaches;
- Immune system disease affecting many organs in the body (systemic lupus erythematosus (SLE));
- Epilepsy;
- Asthma;
- A disease affecting the eardrum and hearing (otosclerosis);
- Very high level of fat in your blood (triglycerides);
- Fluid retention due to heart or kidney problems.

Stop using Intrarosa and refer to a doctor immediately
If you notice any of the following during hormone replacement therapy:
- Any of the conditions mentioned in the section "Do not use the medicine if";
- Yellowing of the skin or whites of the eyes (jaundice). These may be signs of a liver disease;
- If you become pregnant;
- Large increase in blood pressure (symptoms may include headache, fatigue, dizziness);
- Migraine-like headaches that occur for the first time;
- If you notice signs of blood clots, such as:
  - Painful swelling and redness in the legs;
  - Sudden chest pain;
  - Difficulty breathing.

For more information, see "Blood clots in the vein (thrombosis)"

Note: Intrarosa is not a contraceptive. If less than 12 months have passed since your last menstrual period or you are under the age of 50, you may still need to use an additional contraceptive to prevent pregnancy. Consult your doctor.

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

Excessive thickening of the lining of the womb and cancer of the lining of the womb
Taking estrogen-only tablets as long-term hormone replacement therapy may increase the risk of developing cancer of the womb lining. **Intrarosa** does not stimulate the endometrium, which is reflected in the endometrial atrophy observed in all women treated with **Intrarosa** for one year during clinical trials.

It is not known whether there is a risk with long-term use of **Intrarosa** (more than one year). However, it has been observed that **Intrarosa** has very low absorption into the blood, therefore the addition of progestogen is not necessary.

If you suffer from bleeding or have spotting, there is usually no cause for concern, but you should schedule an appointment with your doctor. This may be a sign that your endometrium has thickened.

The following risks apply to medicines that are given as hormone replacement therapy and are found in the bloodstream. However, **Intrarosa** is intended for local vaginal treatment and its absorption into the blood is very low. It is less likely that the conditions mentioned below will worsen or recur during treatment with **Intrarosa**, but you should refer to your doctor if you are concerned.

Breast cancer
Evidence suggest that combined estrogen-progestogen and possibly also estrogen only hormone replacement therapy increases the risk of breast cancer. The additional risk depends on the duration of the hormone replacement therapy. The additional risk becomes apparent within a few years. However, it returns to normal within a few years (5 at the most) after stopping treatment.

- **Check your breasts regularly. Refer to your doctor if you notice any changes such as:**
  - Appearance of dimples in the skin;
  - Changes in the nipple;
  - Appearance of lumps that you can see or feel.

Ovarian cancer
Ovarian cancer is rare – more rare than breast cancer. Use of estrogen alone as hormone replacement therapy 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 hormone replacement therapy, about 2 women in 2,000 will be diagnosed with ovarian cancer over a period of 5 years. For women who have been taking hormone replacement therapy for 5 years, there will be about 3 cases per 2,000 users (i.e., about one additional case). Cases of breast and ovarian cancer have rarely been reported in women treated with 6.5 mg prasterone for 52 weeks.

Effect of hormone replacement therapy on the heart and circulation
Intrarosa has not been studied in women with a history of thromboembolic diseases (formation of blood clots in blood vessels), uncontrolled hypertension or heart disease.

Blood clots in the vein (thrombosis)
The risk of blood clots in the vein is about 1.3 to 3 times higher in hormone replacement therapy users than in non-users, especially during the first year of use.
Blood clots can be severe and if one travels to the lungs, it can cause chest pain, shortness of breath, fainting or even death.

The chance of suffering from a blood clot in the veins increases 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 undergo surgery);
- You are severely overweight (BMI >30 kg/m^2);
- You have any clotting problem that requires long-term treatment with a medicine for preventing blood clots;
- If any of your relatives has ever suffered from blood clots in the leg, lung or other organ;
- You have systemic lupus erythematosus;
- You have cancer.

For signs of a blood clot, see "Stop using **Intrarosa** and see a doctor immediately".
In clinical trials with intravaginal prasterone, no deep vein thrombosis was observed, while there was one case of pulmonary embolism consistent with lower incidence with **Intrarosa** than in the placebo group.

Among women in their 50s who do not receive hormone replacement therapy, on average, over a 5-year period, about 4 to 7 out of 1,000 women are expected to develop a venous blood clot.

Heart disease (heart attack)/hypertension
For women treated with estrogen-only therapy there is no increased risk of developing a heart disease.

Stroke
The risk of stroke is about 1.5 times higher in users of hormone replacement therapy than in non-users. The number of additional cases of stroke following the use of hormone replacement therapy will increase with age.
No case of stroke was observed during the clinical trials with **Intrarosa**.

Among women in their 50s who do not receive hormone replacement therapy, on average, 8 out of 1,000 are likely to suffer a stroke over 5 years. Among women in their 50s who receive hormone replacement therapy, there will be 11 cases out of 1,000 users, over 5 years (i.e., 3 additional cases).

Other conditions
- Hormone replacement therapy will not prevent memory loss. There is evidence of a higher risk of memory loss in women who start receiving hormone replacement therapy after the age of 65. Refer to your doctor for advice.
- You may have vaginal discharge due to melting of the hard fat that forms the base for the pessaries and adds to the increased vaginal discharge following treatment. If vaginal discharge occurs, it is not required to stop using **Intrarosa**.
- **Intrarosa** may damage latex condoms, diaphragms and cervical caps.
- If you have a vaginal infection, you will need to receive antibiotic treatment before using **Intrarosa**.

Children and adolescents

The use of **Intrarosa** is in adult women only.

Drug interactions

If you are taking, have recently taken or might take other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist.

There is no available data on the efficacy and safety in women currently treated with hormone therapy such as: androgens, hormone replacement therapy (estrogen only or in combination with progestogens).

The use of **Intrarosa** in combination with hormone replacement therapy (estrogen only or estrogen-progestogen or androgen therapy) or vaginal estrogens is not recommended.

Pregnancy, breastfeeding and fertility

Pregnancy and breastfeeding
Intrarosa is intended for use in postmenopausal women only. If you become pregnant, stop using **Intrarosa** and refer to your doctor.

Fertility
Intrarosa is not intended for women who can conceive. It is not known if the product affects fertility.

Driving and using machines

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

3. How to use this medicine

Always use this medicine according to the doctor's instructions. Check with the doctor or pharmacist if you are not sure about the dosage and the manner of treatment with the medicine. The dosage and manner of treatment will be determined by the doctor only.
Your doctor will aim to prescribe the lowest dose to treat your symptom for the shortest time necessary. Talk to your doctor if you think this dose is too strong or not strong enough.

The usual recommended dosage is:
Use one vaginal pessary once a day, before bedtime.
Do not exceed the recommended dose.

How to use
Insert the pessary into the vagina with your finger or with the applicator provided in the package.
Do not swallow.

Read the instructions for using **Intrarosa** that appear at the end of the leaflet carefully before using this medicine.

Treatment duration
After initial use, you should refer to your doctor at least every 6 months to check whether you should continue to use **Intrarosa**.

If you used more Intrarosa than you should
Vaginal lavage is recommended.

If you forgot to use the medicine
If you forgot to use the vaginal pessary at the designated time, you should use one as soon as you remember. However, if you need to use the next dose in less than 8 hours, skip the missed pessary. Do not use two pessaries to make up for a forgotten pessary.

Continue with the treatment as recommended by the doctor.
Even if there is an improvement in your health, do not stop taking this medicine without consulting the doctor.

If you need to undergo surgery
If you are going to undergo surgery, tell the surgeon you are using **Intrarosa**. You may need to stop using **Intrarosa** about 4 to 6 weeks before surgery 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.

Do not take medicines in the dark! Check the label and the dose each time you take a medicine. Wear glasses if you need them.
If you have further questions on the use of this medicine, consult the doctor or pharmacist.

4. Side effects

Like any medicine, the use of **Intrarosa** may cause side effects in some users. Do not be alarmed while reading the list of side effects. You may not suffer from any of them.

The following diseases are reported more often in women who are taking hormone replacement therapy, which circulate in the blood, compared to women who are not using hormone replacement therapy. These risks apply less to treatments with vaginally administered estrogen:
- breast cancer;
- ovarian cancer;
- blood clots in the veins of the legs or lungs (venous thrombosis);
- stroke;
- possible memory loss, if hormone replacement therapy is started after the age of 65.

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

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

The following side effects have also been reported:
- **Common side effects** (effects that appear in 1-10 users out of 100): abnormal Pap smear (mainly ASCUS or LGSIL), weight fluctuations (increase or decrease);
- **Uncommon side effects** (effects that appear in 1-10 users out of 1,000): benign cervical or uterine polyps, benign breast lump.

The following side effects have been reported with hormone replacement therapy containing estrogens but not with **Intrarosa** during the clinical trials:
- Gallbladder disease
- Various skin disorders:
  - discoloration of the skin especially of the face or neck known as "pregnancy patches" (chloasma);
  - painful reddish nodules on the skin (erythema nodosum);
  - rash with target-shaped redness or sores (erythema multiforme).

If a side effect appears, if one of the side effects worsens or if you suffer from a side effect which is not mentioned in this leaflet, consult the doctor.

Reporting of side effects
Side effects can be reported to the Ministry of Health via the link "דיווח על תופעות לוואי עקב טיפול תרופתי" that can be found on the home page of the Ministry of Health website (www.health.gov.il) directing to the online form of adverse events reporting or via the following link: https://sideeffects.health.gov.il

5. How to store the medicine

- Avoid poisoning! This medicine and any other medicine must be stored in a closed place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (EXP) stated on the package. The expiry date refers to the last day of that month.
- **Storage conditions:** Store below 25°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. Additional information

In addition to the active ingredient, this medicine also contains hard fat.

What the medicine looks like and what the package contains:
Intrarosa is a white/cream-colored vaginal pessary.

The package contains 28 vaginal pessaries and 6 applicators.

Name of Manufacturer and its address: Endoceutics Inc., Quebec, Canada

Revised in May 2020

Drug registration number at the national drug registry of the Ministry of Health: 163-84-36058-00

Intrarosa PIL PB0420-07

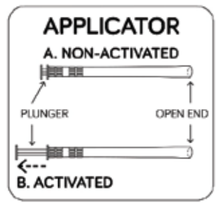
Registration holder: Dexcel® Ltd.
1 Dexcel St., Or Akiva 3060000, Israel

Instructions for use of Intrarosa

How should I use Intrarosa?
- Insert one prasterone pessary into the vagina once a day at bedtime with an applicator or your finger.

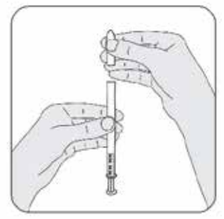
Before you start
- Empty the bladder and wash your hands before using the pessary and applicator.
- Tear off one wrapped pessary from the strip containing 7 vaginal pessaries.

A. Using the applicator

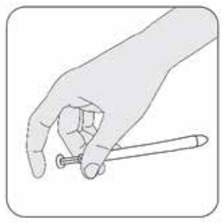


Step 1
1a. Remove one applicator from the package.
1b. Pull the plunger back until it stops in order to activate the applicator. The applicator must be activated before use. Place the applicator on a clean surface.

Step 2
- Slowly pull the plastic tabs on the vaginal pessary away from each other so that the pessary remains without moving in your fingers.
- Carefully remove the pessary from the plastic wrap.
- If the pessary falls on an unsanitary surface, replace it with a new one.



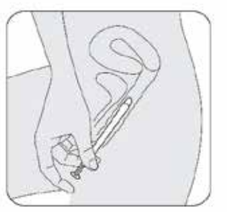
Step 3
- Place the flat end of the pessary inside the open end of the activated applicator as shown earlier. You can now insert the pessary into your vagina.



Step 4
- Hold the applicator between your thumb and middle finger.
- Leave your index finger free to press the plunger of the applicator after the applicator is inserted into the vagina.

Step 5
- Choose the most comfortable position for you to insert the pessary.

5a. Lying position



5b. Standing position

Step 6
- Gently slide the pessary end of the applicator into the vagina as far as it goes in comfortably.

Do not use force.

Step 7
- Press the applicator plunger with your index 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:
  - Separate 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 instructions for step 2 and then gently insert the pessary into the vagina with your finger as far as it goes in comfortably. **Do not use force.**