

PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

The medicine is dispensed with a doctor's prescription only

OVESTIN® CREAM

Estriol 0.1% w/w

The active ingredient and its quantity:

Each gram of cream contains 1 mg Estriol.

One dose (when the amount of cream in the applicator reaches the ring mark) contains 0.5 g Ovestin Cream corresponding to 0.5 mg Estriol.

For a list of inactive and allergens in the preparation, see section 6 “**Further information**”. Also see in section 2 “**Important information regarding some of the ingredients of the medicine**”.

Read this leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, ask the doctor or pharmacist.

- This medicine has been prescribed for your treatment. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.
- If any of the side effects worsen, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

1. WHAT IS THE MEDICINE INTENDED FOR?

The medicine is intended for the treatment of vulvo-vaginal complaints related to estrogen deficiency.

Therapeutic group: Ovestin Cream contains an active ingredient called estriol. It belongs to a group of medicines called **Hormone Replacement Therapy (HRT)**.

Estriol (the active ingredient in Ovestin Cream) is one of the natural estrogens.

- Estrogens are female sex hormones.
- Estrogens are produced in the ovaries.
- Estrogens cause sexual development in women and control the menstrual cycle during the child-bearing years.

When women get older, the ovaries gradually produce less estrogen.

- This process happens at menopause (usually around the age of 50).
- If the ovaries are removed before the menopause, estrogen production stops suddenly.

Shortage of estrogens may cause the vaginal wall to become thin and dry, so that sexual intercourse may become painful and you may get vaginal infections. These problems can be relieved by using medicines like Ovestin Cream, which contains estrogen. Several days or weeks may pass before you notice an improvement.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- you are sensitive (allergic) to the active ingredient estriol or to any of the additional ingredients contained in the medicine (listed in section 6).
- you have or have ever had **breast cancer**, or if you suspect that you have breast cancer.
- you have or suspect that you have an estrogen-sensitive cancer, such as, cancer of the womb lining (endometrium).
- you have **unexplained vaginal bleeding**.
- you have **excessive thickening of the womb lining (endometrial hyperplasia)** that is not being treated.
- you have had or currently have a **blood clot in a vein** (thrombosis), such as in the legs (deep venous thrombosis) or the lungs (pulmonary embolism).
- **you have a blood clotting disorder** (such as protein C, protein S, or antithrombin deficiency).
- you have or recently have had a disease caused by blood clots in the arteries, such as a **heart attack, stroke or angina pectoris**.
- you have or have ever had a **liver disease** and your liver function tests have not returned to normal.
- you have a rare blood problem called “porphyria”, which is inherited.

If any of the above conditions develop for the first time while using Ovestin Cream, stop using the medicine immediately and consult your doctor immediately.

Special warnings regarding use of the medicine

Before treatment with Ovestin Cream, tell your doctor if you have or have had in the past any of the following problems, since they can recur or worsen during the course of treatment with Ovestin Cream. If so, you should be checked by the doctor more frequently:

- fibroids in the womb
- growth of the womb lining outside the 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]” section)
- increase risk of developing an estrogen-sensitive cancer (such as when there is a mother, sister or grandmother who had breast cancer)
- high blood pressure
- liver problems, such as a benign liver tumor
- diabetes
- gallstones
- migraine or severe headaches
- an immune system problem called “systemic lupus erythematosus” (SLE) that affects many organs of the body
- epilepsy
- asthma
- a disease affecting the eardrum and hearing (otosclerosis)
- fluid retention due to cardiac or kidney problems.

Tell the doctor if you have hepatitis C and you are taking a combination of the following medicines: ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. Taking a combination of these medicines with estrogen-containing preparations may cause increases in liver function blood test results (increase in ALT liver enzyme); the risk of this happening with Ovestin Cream is currently unknown.

Stop using Ovestin Cream immediately and see a doctor as soon as possible

If you notice any of the following signs while using HRT:

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

For more information, see “Blood clots in a vein (thrombosis)”.

Note: Ovestin Cream is not a contraceptive. If less than 12 months have passed since your last menstrual period or you are under 50 years of age, you will still need to use additional contraception to prevent pregnancy. Consult with your doctor.

HRT and cancer

Excessive thickening of the lining of the womb – (endometrial hyperplasia) and cancer of the lining of the womb (endometrial cancer)

Taking estrogen-only HRT tablets for a long time can increase the risk of developing cancer of the womb lining (the endometrium). It is uncertain whether there is a similar risk when using Ovestin Cream if used for repeated or long-term (more than one year) treatments. However, Ovestin Cream has shown very low absorption into the blood; therefore, the addition of a progestogen is not necessary.

If you have bleeding or spotting, it usually is not a reason for concern, but you should speak to 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, Ovestin Cream 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 recur during treatment with Ovestin Cream, but refer to your doctor if you are concerned.

Breast cancer

Evidence suggests that use of Ovestin Cream does not increase the risk of breast cancer in women who did not have breast cancer in the past. It is not known if Ovestin Cream can be safely used in women who had breast cancer in the past.

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

- dimpling of the skin
 - changes in the nipple
 - any lump you can see or feel
- Additionally, mammography screening is recommended.

Ovarian cancer

Ovarian cancer is rare, much rarer than breast cancer.

The use of estrogen-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 50-54 who are not taking HRT, about 2 women in 2,000 will be diagnosed with ovarian cancer over a 5-year period. Among women who have been taking HRT for 5 years, there will be about 3 cases per 2,000 users (i.e., about 1 extra case per 2,000 users).

Effect of HRT on your heart or circulation

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 use.

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

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

- you are unable to walk for a long time because of major surgery, injury or illness (see also “Operations” in section 2).
- if you are seriously overweight (BMI > 30 kg/m²).
- you have a blood clotting problem that requires 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 legs, lungs or another organ
- if you have “systemic lupus erythematosus” (SLE)
- if you have cancer.

For signs of a blood clot, see “Stop using Ovestin Cream immediately and see a doctor as soon as possible”.

Comparison

Looking at women in their 50s who are not taking HRT, on average, over a 5-year period, 4 to 7 cases in 1,000 women are expected to get a blood clot in a vein. For women in their 50s who have been taking estrogen-only HRT for 5 years, there will be 5 to 8 cases in 1,000 users (i.e., 1 extra case for every 1,000 users).

Heart disease (heart attack)

For women taking estrogen-only therapy, there is no increased risk of developing a heart disease.

Stroke

The risk of getting a 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.

Comparison

Looking at women in their 50s who are not taking HRT, on average, 8 in 1,000 are expected to have a stroke within a 5-year period. For women in their 50s who are taking HRT, there will be 11 cases in 1,000 users, within 5 years (i.e., an extra 3 cases in every 1,000 users).

Other conditions

HRT will not prevent memory loss. There is evidence of a higher risk of memory loss in women who started using HRT after the age of 65. Consult your doctor.

Medical history and routine checkups

Use of HRT carries risks which should be taken into account when considering whether to start or continue treatment.

There is limited experience in treatment of women with early menopause (due to ovarian failure or surgery). If you are experiencing early menopause, the risks of using HRT may be different. Consult your doctor.

Before you start (or resume) taking HRT, your doctor will ask you about your personal and family medical history. Your doctor may decide to perform a physical examination. This can include a breast examination and/or internal examination, if needed.

Once you start treatment with Ovestin Cream, visit your doctor for routine checkups (at least once a year). At these checkups, your doctor may discuss the benefits and risks of continued use of Ovestin Cream.

Regular breast screening should be performed as recommended by your doctor.

Drug interactions

If you are taking or have recently taken other medicines including non-prescription medicines and nutritional

supplements, tell the doctor or the pharmacist.

This is because Ovestin Cream can affect the way some other medicines work. Also, some other medicines can affect the way Ovestin Cream works. **Tell your doctor** or pharmacist if you are taking any of the following medicines:

- medicines for epilepsy - such as barbiturates, hydantoins and carbamazepine.
- medicines for infections - such as griseofulvin and rifamycins.
- medicines for viral infections - such as nevirapine, efavirenz, ritonavir or nelfinavir.
- herbal preparations containing St. John's wort (*Hypericum perforatum*) - an herbal medicine used to treat depression.
- any one of the following medicines: corticosteroids, succinylcholine, theophylline or toleandomycin.

Tell the doctor if you have Hepatitis C and if you are taking the combination of the following medicines ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. Taking the combination of these medicines with estrogen-containing preparations may cause increases in liver function blood test results (increase in ALT liver enzyme); the risk of this happening with Ovestin Cream is currently unknown. If you are not sure if the above is relevant to you, talk to your doctor before using Ovestin Cream.

If you have a vaginal infection, it should be treated before using Ovestin Cream.

Operations

If you are about to undergo surgery, **tell your doctor** you are using Ovestin Cream. You may need to stop using HRT for about 4 to 6 weeks before the operation to reduce the risk of a blood clot. Your doctor will tell you when you can start using HRT again.

Pregnancy and breastfeeding

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

- Do not use Ovestin Cream if you are pregnant or may be pregnant. This is because it may affect the baby.
- Do not breastfeed if you are using this medicine.

If you are pregnant or breastfeeding, ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Ovestin Cream has no effect or may have little effect on the ability to drive or use machines.

Important information regarding some of the ingredients of the medicine

Ovestin Cream contains cetyl alcohol and stearyl alcohol. These can cause localized skin reactions (for example, contact dermatitis).

3. HOW SHOULD YOU USE THE MEDICINE?

Always use Ovestin Cream according to the doctor's instructions. You should check with the doctor or pharmacist if you are not sure about the dosage and treatment regimen of the medicine.

- If you have had your womb and ovaries removed, you can start using Ovestin Cream straight away.
- If you have never used HRT before or if you are changing over from a period-free-type HRT, you can start using Ovestin Cream straight away.
- If you are changing over from another type of HRT during which you have a period, start taking Ovestin Cream one week after you finish the other HRT.

The dosage and duration of treatment will be determined by the doctor only.

Do not exceed the recommended dose.

Note: This medicine is intended for vaginal use.

The recommended dosage is generally:

For vaginal problems

- The usual dose is 1 applicator filled up to the ring mark (0.5 mg estriol in 0.5 g of cream) a day, for the first 2 to 3 weeks.
- Then, the dose is 1 applicator filled up to the ring mark, twice a week.

Your doctor will prescribe the lowest dose that relieves your symptoms. Your doctor may want you to stop the treatment from time to time (every 2-3 months, for a period of 4 weeks). This is to check if you still need treatment.

Instructions for use:

Ovestin Cream comes in a package that includes a clear plastic applicator.

Use the applicator to apply the cream in the vagina. **A good time to do this is before going to bed.**

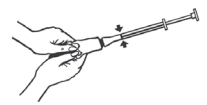
The applicator has a ring marked on the body. Fill the applicator up to the ring mark with Ovestin Cream to get the correct dose.

Follow these instructions:

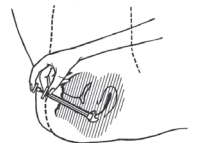
1. Remove the cap from the tube and turn the cap upside down. Then use the sharp point on the cap to open the tube.
2. Screw the end of the applicator onto the tube.



3. Squeeze the tube to fill the applicator with the cream, up to the red ring mark (the plunger will stop at the red ring mark).



4. Unscrew the applicator from the tube and close the tube with the cap.
5. To apply the cream, lie down on your back, put the end of the applicator deep into your vagina and slowly push the plunger all the way in.



Cleaning the applicator

- After use, pull the plunger out of the barrel.
- Wash the plunger and barrel with warm, soapy water.
- Do not use detergents. Rinse well with clean water afterwards.
- Do not put the applicator in boiling water.

Ovestin Cream is easily removed with water.

If you accidentally applied a higher dosage or if you or someone else accidentally swallowed the medicine, there is no need to worry. However, you should talk to your doctor, since you may feel nauseous or vomit. Some vaginal bleeding may appear after a few days.

If you took an overdose or if a child or anyone else has accidentally swallowed the medicine, refer immediately to a doctor or proceed to a hospital emergency room and bring the package of the medicine with you.

If you forgot to take the medicine

If you forgot to take this medicine at the required time, do not take a double dose.

- Apply the missed dose when you remember, unless you are more than 12 hours after the scheduled time.
- If you are more than 12 hours late, just skip the missed dose.

Adhere to the treatment as recommended by the doctor.

Even if there is an improvement in your health, do not stop treatment with this medicine without consulting your doctor.

If you stop taking the medicine

Keep using this medicine as prescribed for you by the doctor, even if you seem to feel better. If you stop too early or suddenly, your problem may return.

Do not take medicines in the dark! Check the label and the dose each time you take medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult the doctor or the pharmacist.

4. SIDE EFFECTS

Like all medicines, use of Ovestin Cream may cause side effects in some users.

Do not be alarmed by the list of side effects. You may not suffer from any of them.

The following diseases are reported more often in women using HRT which circulate in the blood compared to women not using HRT. These risks apply less to vaginal treatments such as Ovestin Cream:

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

See further information about these side effects in section 2.

Refer to the doctor straight away, if you notice any of the following serious side effects – your doctor may decide to discontinue use of the cream:

- your blood pressure rises
- your skin or the “whites” of your eyes become yellow (jaundice)
- you suddenly have migraine-type headaches
- you have signs of a blood clot
- you have one or more of the problems listed in section 2 (see above).

These side effects are rare.

Additional side effects:

- irritation or itching of the skin in or around your vagina when you start using Ovestin Cream. This effect usually gets better after a few weeks

- increased vaginal discharge, bleeding or spotting
- gallbladder problems
- skin problems such as a rash or an allergy (sensitivity) to the sun
- breasts become swollen, tender or painful
- headaches
- nausea or vomiting
- flu-like symptoms.

Tell your doctor if you get any of these side effects; he may decide to stop the treatment for a while.

Dementia

HRT will not prevent memory loss. In one study of women who started treatment with combined HRT after the age of 65, a small increase in the risk of dementia was observed.

If a side effect occurs, if one of the side effects worsens, or if you suffer from a side effect not mentioned in the leaflet, consult with the doctor.

The following side effects have been reported with other HRTs:

- gallbladder disease
- various skin problems:
 - discoloration of the skin, especially of the face or neck, known as “pregnancy patches” (chloasma)
 - painful and reddish blisters on the skin (erythema nodosum)
 - rash with target-shaped reddening or sores (erythema multiforme).

Reporting side effects:

Side effects can be reported to the Ministry of Health by clicking on the link “Report Side Effects of Drug Treatment” found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: <https://sideeffects.health.gov.il>

In addition, you can report to Padagis via the following address: Padagis.co.il

5. HOW SHOULD THE MEDICINE BE STORED?

• Avoid poisoning! This medicine, and any other medicine, should be kept in a safe place out of the reach and sight of children and/or infants in order 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. date) that appears on the package. The expiry date refers to the last day of that month.

• **Storage conditions:** Store below 25°C. Do not freeze. Can be used within 35 days of first opening, and no later than the expiration date of the medicine, whichever comes first.

• Do not dispose of medicines into wastewater or household waste. Ask the pharmacist how to dispose of medicines no longer in use. These measures will help protect the environment.

6. FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains inactive ingredients:

Purified water, glycerol, stearyl alcohol, octyldodecanol, cetyl alcohol, polysorbate 60, cetyl palmitate, sorbitan stearate, lactic acid, chlorhexidine dihydrochloride, sodium hydroxide.

What the medicine looks like and contents of the package:

Ovestin Cream is a homogeneous, smooth, white to almost-white mass of creamy consistency, with a mild characteristic odor. Ovestin Cream is contained in a 15-gram aluminum tube.

Each tube is packed in a cardboard package containing a transparent plastic applicator.

Registration Holder and address: Padagis Israel Agencies Ltd., 1 Rakefet St., Shoham.

Manufacturer name and address: Aspen Pharma Trading Ltd., Dublin, Ireland.

Revised in October 2023 according to MOH guidelines.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 6560.21266