

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ovestin 1mg per gram, vaginal cream

Estriol

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Ovestin is and what it is used for
2. What you need to know before you use Ovestin
3. How to use Ovestin
4. Possible side effects
5. How to store Ovestin
6. Contents of the pack and other Information

1. What Ovestin is and what it is used for

Ovestin belongs to a group of medicines called vaginal Hormone Replacement Therapy (HRT). It contains the female hormone estriol (an estrogen). Ovestin is used in postmenopausal women with at least 12 months since their last period.

It is used to relieve menopausal symptoms in the vagina such as dryness or irritation. In medical terms this is known as 'vaginal atrophy'. It is caused by a drop in the levels of oestrogen in your body. This happens naturally after the menopause.

The active substance of Ovestin is estriol, one of the natural estrogens produced by the body (female sex hormones). Estrogens are mainly produced in the ovaries. They are necessary for the normal sexual development of women and for the regulation of the menstrual cycle during the childbearing years. When women get older the ovaries gradually produce less estrogen. The period in which this happens (usually around the age of 50) is called the menopause. If the ovaries are removed surgically (ovariectomy) before the menopause, the decrease in estrogen production occurs very abruptly.

The shortage of estrogens during menopause may cause the vaginal wall to become thin and dry. As a result, sexual intercourse may become painful and vaginal itching and infections may occur. Estrogen deficiency may also lead to symptoms like urinary incontinence and recurrent cystitis.

Ovestin works by replacing the oestrogen which is normally produced in the ovaries of women. It is inserted into your vagina, so the hormone is released where it is needed. This may relieve discomfort in the vagina. It may take several days or even weeks before you notice an improvement.

In addition to the above-mentioned uses Ovestin cream may also be prescribed to:

- improve wound healing in postmenopausal women undergoing vaginal surgery

Ovestin cream can easily be removed with water.

2. What you need to know before you use Ovestin

Medical history and regular check-ups

The use of HRT carries risks which need to be considered when deciding whether to start taking it or whether to carry on taking it.

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

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

Once you have started on Ovestin you should see your doctor for regular check-ups (at least once a year). At these check-ups, discuss with your doctor the benefits and risks of continuing with Ovestin.

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

Do not use Ovestin

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

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

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

Warnings and precautions

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

- increased risk of developing blood clots (see "Blood Clots in a vein (thrombosis)")
- high blood pressure

- migraine or severe headaches;
- epilepsy
- asthma
- a liver disorder, such as a benign liver tumour
- growth of womb lining outside your womb (endometriosis) or a history of excessive growth of the womb lining (endometrial hyperplasia)
- fibroids inside your womb
- increased risk of getting an estrogen-sensitive cancer (such as having a mother, sister or grandmother who has had breast cancer)
- diabetes
- gallstones
- a disease of the immune system that affects many organs of the body (systemic lupus erythematosus, SLE)
- a disease affecting the eardrum and hearing (otosclerosis)
- fluid retention due to cardiac or kidney problems

Tell your doctor if you have Hepatitis C and you are taking the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. Taking the combination of these drugs with some oestrogen-containing products may cause increases in liver function blood test results (increase in ALT liver enzyme); the risk of this happening with Ovestin is currently unknown.

Tell your doctor if you notice any change in your condition while using Ovestin

Stop using Ovestin and see a doctor immediately if you notice any of the following when taking HRT:

- any of the conditions mentioned in the ‘DO NOT take Ovestin’ section
- yellowing of your skin or the whites of your eyes (jaundice). These may be signs of a liver disease.
- a large rise in your blood pressure (symptoms may be headache, tiredness, dizziness)
- migraine-like headaches which happen for the first time
- if you become pregnant

If you notice signs of a blood clot, such as:

- painful swelling and redness of the legs
- sudden chest pain
- difficulty in breathing

For more information, see ‘Blood clots in a vein (thrombosis)’.

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

HRT and cancer

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

Taking oestrogen-only HRT tablets for a long time can increase the risk of developing cancer of the womb lining (the endometrium).

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

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

To prevent endometrial stimulation the maximum dose should not be exceeded nor should the maximum dose be used for longer than four weeks.

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

Breast cancer

Evidence suggests that using Ovestin does not increase the risk of breast cancer in women who had no breast cancer in the past. It is not known if Ovestin 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 lumps you can see or feel

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

Ovarian cancer

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

The risk of ovarian cancer varies with age. For example, in women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period. For women who have been taking HRT for 5 years, there will be about 3 cases per 2000 users (i.e. about 1 extra case).

Effects 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 taking it.

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

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

- you are unable to walk for a long time because of major surgery, injury or illness (see also section 3, if you need to have surgery)
- you are seriously overweight (BMI >30kg/m²)
- you have any blood clotting problems that needs long-term treatment with a medicine used to prevent blood clots
- If any of your close relatives has ever had a blood clot in the leg, lung or another organ
- you have systemic lupus erythematosus (SLE)
- you have cancer

For signs of a blood clot, see “Stop taking Ovestin and see a doctor immediately”.

Compare

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

have been taking estrogen-only HRT for over 5 years, there will be 5 to 8 cases in 1000 users (i.e. 1 extra case).

Heart Disease (heart attack)

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

Stroke

The risk of getting stroke is about 1.5 times higher in HRT users than in non-users. The number of extra cases of stroke due to use of HRT will increase with age.

Compare

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

Other conditions

HRT will not prevent memory loss. There is some evidence of a higher risk of memory loss in women who start using HRT after the age of 65. Speak to your doctor for advice.

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained without a prescription, herbal medicines or other natural products.

Some medicines may interfere with the effect of Ovestin, or Ovestin may interfere with the effect of other medicines. This might lead to irregular bleeding. This applies to the following medicines:

- Medicines for **epilepsy** (such as phenobarbital, phenytoin and carbamazepine)
- Medicines for **tuberculosis** (such as rifampicin, rifabutin)
- Medicines for **HIV infection** (such as nevirapine, efavirenz, ritonavir and nelfinavir)
- Herbal remedies containing **St John's Wort** (*Hypericum Perforatum*)

Tell your doctor if you have Hepatitis C and you are taking the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. Taking the combination of these drugs with some oestrogen-containing products may cause increases in liver function blood test results (increase in ALT liver enzyme); the risk of this happening with Ovestin is currently unknown.

Laboratory tests

If you need a blood test, tell your doctor or the laboratory staff that you are using Ovestin, because this medicine can affect the results of some tests.

Using Ovestin with food and drink.

You can eat and drink normally while you're using Ovestin.

Pregnancy and breast-feeding

Ovestin is for use in postmenopausal women only.

If you become pregnant, stop taking Ovestin and contact your doctor.

If you are breast-feeding, do not use Ovestin without asking your doctor first.

Driving and using machines

Ovestin is not expected to affect your ability to drive a car or operate machinery. However, individual responses to medication may vary.

Important information about some of the ingredients of Ovestin.

Ovestin cream contains cetyl alcohol and stearyl alcohol. This may cause local skin reactions (e.g. contact dermatitis).

3. How to use Ovestin

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

For vaginal complaints the usual dose is 1 applicator - dose (0.5 mg estriol in 0.5 g of cream) daily during the first weeks (maximally 4 weeks). Later on the dose is gradually decreased to, for instance, 1 applicator-dose twice a week. Your doctor will prescribe the lowest dose that relieves your symptoms.

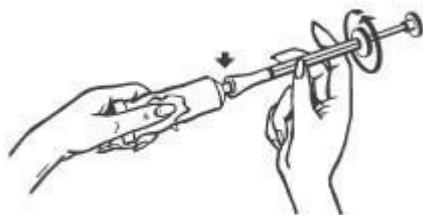
Your doctor may want you to stop from time to time (every 2 to 3 months), to check if you still need treatment. Do not stop just because your complaints have disappeared, but keep using this medicine as prescribed by your doctor. If you stop too early or too suddenly your complaints may return.

For improving wound healing in postmenopausal women undergoing vaginal surgery the usual dose is 1 applicator-dose (0.5 mg estriol in 0.5 g of cream) daily for 2 weeks before the operation. In the two weeks after vaginal surgery, the dose is 1 applicator-dose twice a week.

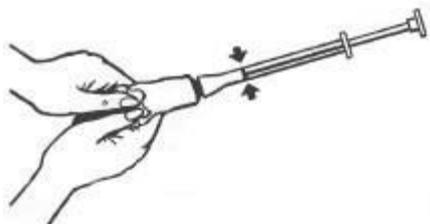
Use the applicator to apply the cream in the vagina. It is a good idea to do this before going to bed.

One application (applicator filled to the ring mark) contains 0.5 gram Ovestin cream, which contains 0.5 mg estriol.

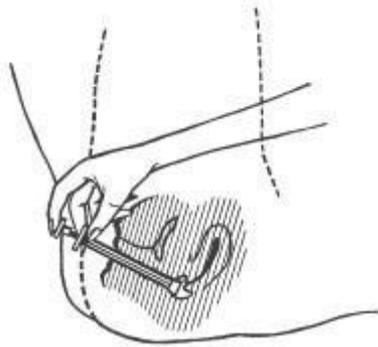
- 1 Remove cap from the tube, invert it, and use the sharp point to open the tube.
2. Screw the end of the applicator onto the tube. Make sure the plunger is fully inserted into the barrel.



3. Squeeze tube slowly to fill the applicator with the cream until the plunger stops (at the red ring, see arrows in picture below).



4. Unscrew applicator from tube and put cap back on tube.
5. To apply the cream, lie down and insert the end of the applicator deep into the vagina.
6. Slowly push plunger all the way in until the applicator is empty.



7. After use, pull plunger out of barrel beyond the point of resistance and wash both in warm, soapy water.

Do not use detergents. Rinse well afterwards.

DO NOT PUT THE APPLICATOR IN HOT OR BOILING WATER.

8. The applicator can be re-assembled by fully inserting the plunger into the barrel beyond the point where resistance is felt.

Discard the applicator once the tube is empty.

Your doctor will aim to prescribe the lowest dose to treat your symptoms for as short as necessary. Speak to your doctor if you think this dose is too strong or not strong enough.

If you have the impression that the effect of Ovestin is too strong or too weak, talk to your doctor.

If you use more Ovestin than you should:

If you have used more Ovestin than you should, talk to a doctor or pharmacist. If someone has swallowed some cream, there is no need for great concern. However, you should tell a doctor. Symptoms you might notice are nausea and vomiting. In females vaginal bleeding may occur after a few days.

If you forget to use Ovestin

Do not use a double dose to make up for a forgotten 1 dose.

If you forgot to administer a dose, administer the missed dose as soon as you remember, unless you are more than 12 hours late. If you are more than 12 hours late, do not administer the missed dose, and just carry on with the next dose as normal.

If you need to have surgery

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

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible Side Effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following diseases are reported more often in women using HRT. These risks apply less to vaginally administered treatments such as Ovestin:

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

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

Dependent on dosage and sensitivity of the patient. Ovestin may sometimes cause side effects, such as:

- swelling and increased tenderness of the breasts
- minor vaginal bleeding
- increased vaginal discharge
- nausea
- fluid retention in the tissues, usually marked by swollen ankles or feet
- local irritation or itching
- flu-like symptoms

In most patients these side effects will disappear after the first weeks of treatment.

The following side effects have been reported with other HRTs:

- gall bladder disease
- various skin disorders
 - discolouration of the skin especially of the face or neck known as “pregnancy patches” (chloasma),
 - painful reddish skin nodules (erythema nodosum)
 - rash with target-shaped reddening or sores (erythema multiforme)
- may cause local skin reactions (e.g. contact dermatitis)

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system:

HPRA Pharmacovigilance
 Earlsfort Terrace
 Dublin 2
 Ireland
 Tel: +353 1 6764971
 Fax: +353 1 6762517
 Website: www.hpra.ie
 e-mail: medsafety@hpra.ie

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ovestin

Keep this medicine out of the sight and reach of children.

Store below 25°C. Do not freeze.

Do not use Ovestin after the expiry date which is stated on the package, after “Expiry date” or “Exp”. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further Information

What Ovestin contains

The active substance of Ovestin cream is estriol. 1 gram of Ovestin cream contains 1 mg of estriol.

The other ingredients are octyldodecanol, cetyl palmitate, glycerol, cetyl alcohol, stearyl alcohol, polysorbate 60, sorbitan stearate, lactic acid, chlorhexidine dihydrochloride, sodium hydroxide and purified water.

What Ovestin looks like and contents of the pack

Homogeneous, smooth, white to nearly white mass of creamy consistency. Ovestin cream is filled into a 15 gram collapsible aluminum tube. Each tube is packed, together with a CE marked applicator in a cardboard box.

Marketing Authorisation Holder:

Aspen Pharma Trading Limited, 3016 Lake Drive, Citywest Business Campus, Dublin 24, Ireland

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Manufacturer of Ovestin cream:

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This leaflet was last revised in September 2020.