Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ovestin 1mg per gram Vaginal Cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Vaginal cream containing 1 mg estriol in 1 g of cream.

Excipient(s) with known effect:
Cetyl alcohol 36.7 mg per 1 g cream and stearyl alcohol 88.4 mg per 1g cream

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Vaginal cream with applicator.

Ovestin cream is a homogeneous, smooth, white to nearly white mass of creamy consistency.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of vaginal oestrogen deficiency symptoms:

- Treatment of symptoms of vaginal atrophy due to oestrogen deficiency in postmenopausal women.
- Pre and post operative therapy in post-menopausal women undergoing vaginal surgery.

4.2 Posology and method of administration

- For atrophy of the lower urogenital tract:

  1 application per day for the first weeks (maximally 4 weeks), followed by a gradual reduction, based on relief of symptoms, until a maintenance dosage (e.g. 1 application twice a week) is reached.

- As pre- and postoperative therapy in postmenopausal women undergoing vaginal surgery:

  1 application per day in the 2 weeks before surgery: 1 application twice a week in the 2 weeks after surgery.

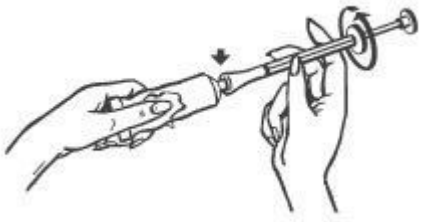
A missed dose should be administered as soon as remembered, unless the missed dose is noticed at the day of the next dose. In the latter case the missed dose should be skipped and the regular dosing scheme continued. Two doses must never be administered on the same day.

Method of administration
Ovestin Cream should be administered intravaginally by means of a calibrated applicator before retiring at night.

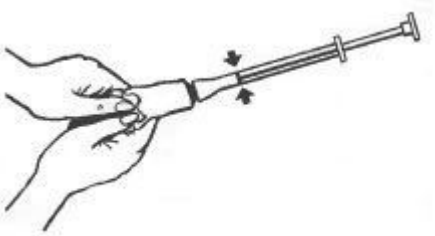
1 applicator-dose (applicator filled to the ring mark) contains 0.5 g Ovestin Cream which corresponds to 0.5 mg estriol.

The following 'Instructions for Use' should be given to the patient and are included in the package leaflet:

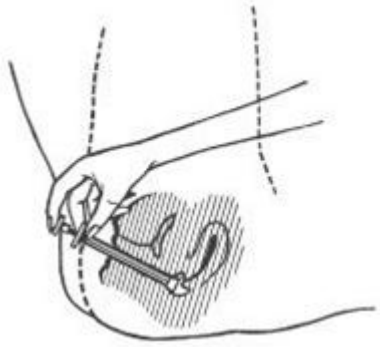
Instructions for Use
1. Remove the cap from the tube, invert it, and use the sharp point to open the tube.
2. Screw the end of the applicator onto the tube.



3. Squeeze tube to fill the applicator with the cream until the plunger stops.



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



After use, pull the plunger out of the barrel and wash both in warm, soapy water. Do not use detergent. Rinse well afterwards.

DO NOT PUT THE APPLICATOR IN HOT OR BOILING WATER.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration of time (see also Section 4.4) should be used.

For Ovestin vaginal cream and pessaries, the systemic exposure of estriol remains closely to the normal postmenopausal range when used in a twice weekly administration, it is not recommended to add a progestagen (but see section 4.4).

In women not taking HRT or women who switch from a continuous combined HRT product, treatment with Ovestin may be started on any day. Women who switch from cyclic HRT regimen should start Ovestin treatment one week after completion of the cycle.

4.3 Contraindications

- Known, past or suspected breast cancer;
- Known or suspected estrogen-dependent malignant tumors (e.g. endometrial cancer);
- Undiagnosed genital bleeding;
- Untreated endometrial hyperplasia;
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism);
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4);
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction);
- Acute liver disease, or a history of liver disease as long as liver function tests failed to return to normal;
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- Porphyria

4.4 Special warnings and precautions for use

- For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.
- Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

Medical examination/follow-up

- Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breast should be reported to their doctor or nurse (see 'Breast cancer' below). Investigations, including appropriate imaging tools, e.g. mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision

- If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Ovestin, in particular:

  - Leiomyoma (uterine fibroids) or endometriosis
  - Risk factors for, thromboembolic disorders (see below)
  - Risk factors for estrogen dependent tumours, e.g. 1st degree heredity for breast cancer
  - Hypertension
  - Liver disorders (e.g. liver adenoma)
  - Diabetes mellitus with or without vascular involvement
  - Cholelithiasis
  - Migraine or (severe) headache
  - Systemic lupus erythematosus
  - A history of endometrial hyperplasia (see below)
  - Epilepsy
  - Asthma
  - Otosclerosis

Reasons for immediate withdrawal of therapy:
Therapy should be discontinued in case a contra-indication is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache
- Pregnancy

Endometrial hyperplasia and carcinoma

- In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when systemic oestrogens are administered alone for prolonged periods.

- For Ovestin vaginal cream and pessaries, the systemic exposure of estriol remains closely to the normal postmenopausal range when used in a twice weekly administration, it is not recommended to add a progestagen.

- Endometrial safety of long-term (more than one year) or repeated use of local vaginally administered oestrogen is uncertain. Therefore, if repeated, treatment should be reviewed at least annually.

- Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore caution is advised when using this product in women who have undergone hysterectomy because of endometriosis, especially if they are known to have residual endometriosis

- If bleeding or spotting appears at any time on therapy, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

The risk of endometrial hyperplasia and carcinoma is increased when systemic estrogens are administered alone for prolonged periods of time.

In order to prevent endometrial stimulation, the daily dose should not exceed 1 application (0.5 mg estriol) nor should this maximum dose be used for longer than a maximum of 4 weeks. One epidemiological study has shown that long-term treatment with low doses of oral estriol, but not vaginal estriol, may increase the risk for endometrial cancer. This risk increased with the duration of treatment and disappeared within one year after the treatment was terminated. The increased risk mainly concerned less invasive and highly differentiated tumors. Therefore if repeated, treatment should be reviewed at least annually, with special consideration given to any symptoms of endometrial hyperplasia or carcinoma.

Breast cancer

- Epidemiological evidence from a large meta-analysis suggests no increase in risk of breast cancer in women with no history of breast cancer taking low dose vaginally applied oestrogens. It is unknown if low dose vaginal oestrogens stimulate recurrence of breast cancer.
- HRT may increase mammographic density. This may complicate the radiological detection of breast cancer. Clinical studies reported that the likelihood of developing increased mammographic density was lower in subjects treated with estriol than in subjects treated with other estrogens.

- It is unknown whether Ovestin carries the same risk. In several population-based case-control studies, estriol was found not to be associated with an increased risk of breast cancer, in contrast to other estrogens. However, the clinical implications of these findings are as yet unknown. Therefore, it is important that the risk of being diagnosed with breast cancer is discussed with the patient and weighed against the known benefits of HRT.

Ovarian cancer

Ovarian cancer is much rarer than breast cancer.
Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only **systemic** HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.

Venous thromboembolism

- **Systemic** HRT is associated with a 1.3-3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see Section 4.8).
- Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).
- Generally recognized risk factors for VTE include use of estrogens, older age, major surgery, prolonged immobilization obesity (BMI > 30 kg/m^2), pregnancy/postpartum period, systemic lupus erythematosus (SLE). There is no consensus about the role of varicose veins in VTE.
- As in all postoperative patients, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilization is to follow elective surgery temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.
- If Ovestin is used for the indication 'pre-and post operative therapy.....' consideration should be given to prophylactic treatment against thrombosis.
- In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening). If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g, antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.
- Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT

- If VTE develops after initiating Ovestin therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnea).

Coronary artery disease (CAD)

Estrogen-only
Randomised controlled data found no increased risk of CAD in hysterectomised women using **systemic** estrogen-only therapy.

Isachaemic stroke

- **Systemic** estrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see section 4.8).

Other conditions

- Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.
- Women with pre-existing hypertriglyceridaemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.
- Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin).
- HRT use does not improve cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined or estrogen-only HRT after the age of 65.
- Ovestin cream contains cetyl alcohol and stearyl alcohol. This may cause local skin reactions (e.g. contact dermatitis).

Concomitant use of Hepatitis C medications

- During clinical trials with the combination drug regimen ombitasvir hydrate/paritaprevir hydrate/ritonavir with or without dasabuvir, ALT elevations to greater than 5 times the upper limit of normal (ULN) were significantly more frequent in female subjects using ethinyl estradiol-containing medications. Women using estrogens other than ethinyl estradiol, such as estradiol, estriol and conjugated estrogens had a rate of ALT elevation similar to those not receiving any estrogens; however, due to the limited number of subjects taking these other estrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir hydrate/paritaprevir hydrate/ritonavir with or without dasabuvir. (See section 4.5.)

4.5 Interaction with other medicinal products and other forms of interactions

Due to the vaginal administration and minimal systemic absorption, it is unlikely that any clinically relevant drug interactions will occur with Ovestin. However interactions with other locally applied vaginal treatments should be considered. There are strong indications that estrogens, estriol included, can increase the pharmacological effects of certain drugs, including corticosteroids, succinylcholine, theophyllines and troleandomycin. If necessary, the dosage of these drugs should be reduced.

Although data are limited, interactions between Ovestin and other medicinal products may occur. The following interactions have been described with use of combined oral contraceptives which may also be relevant for Ovestin.

The metabolism of estrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. barbiturates (primidone included), hydantoins), activated charcoal, anti-infectives (e.g. griseofulvin, rifampicins, the antiretroviral agents nevirapine and efavirenz) and herbal preparations containing St John's wort (Hypericum Perforatum).

Clinically, an increased metabolism of estrogens may lead to decreased effectiveness of Ovestin and changes in uterine bleeding profile.

Conversely, estriol may possibly increase the effectiveness of beta-adrenergic blockers and change the effectiveness of insulins.

During clinical trials with the combination drug regimen ombitasvir hydrate/paritaprevir hydrate/ritonavir with or without dasabuvir, ALT elevations to greater than 5 times the upper limit of normal (ULN) were significantly more frequent in female subjects using ethinyl estradiol-containing medications. Women using estrogens other than ethinyl estradiol, such as estradiol, estriol and conjugated estrogens had a rate of ALT elevation similar to those not receiving any estrogens; however, due to the limited number of subjects taking these other estrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir hydrate/paritaprevir hydrate/ritonavir with or without dasabuvir. (See section 4.4.)

4.6 Fertility, pregnancy and lactation

Fertility
Ovestin is intended for the treatment of post-menopausal (naturally and surgically induced) women only.

Pregnancy and Lactation
Use in pregnancy, suspected pregnancy, or in women breast feeding infants is contraindicated.

4.7 Effects on ability to drive and use machines

There is no information to suggest that Ovestin affects a patient's ability to drive or operate machinery.

4.8 Undesirable effects

From literature and safety surveillance monitoring, the following adverse reactions have been reported:

System organ class	Adverse reactions
General disorders and administration site conditions	Application site pruritus, vaginal burning sensation and vaginal discharge. Flu-like symptoms
Reproductive system and breast disorders	Breast discomfort and pain

These adverse reactions are usually transient, but may also be indicative of too high a dosage.

Class effects associated with systemic HRT
The following risks have been associated with systemic HRT and apply to a lesser extent for Ovestin vaginal cream and pessaries of which the systemic exposure to estriol remains closely to the normal postmenopausal range when used in a twice weekly administration.

- **Ovarian cancer**

Use of systemic HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see Section 4.4).
A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using systemic HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56).
For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

- **Risk of venous thromboembolism**

Systemic HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HT (see section 4.4). Results of the WHI studies are presented:

WHI studies - Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users
Oral estrogen-only*			
50-79	7	1.2 (0.6 - 2.4)	1 (-3 - 10)

* Study in women with no uterus

Risk of ischaemic stroke

- The use of estrogen-only and estrogen-progestagen therapy is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.
- This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age, see section 4.4.

WHI studies combined - Additional risk of isachaemic stoke* over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ration and 95%CI	Additional cases per 1000 HRT users over 5 years
50-79	8	1.3 (1.1 – 1.6)	3 (1 - 5)

* no differentiation was made between ischaemic and haemorrhagic stroke.

Other adverse reactions have been reported in association with **systemic** estrogen-only and estrogen-progestagen combined treatment.

- Estrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer. For further information see sections 4.3 and 4.4
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia over the age of 65 (see Section 4.4)
- Vaginal bleeding after treatment with Ovestin has only rarely been reported.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
HPRA Pharmacovigilance
Earlsfort Terrace
Dublin 2
Ireland
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

4.9 Overdose

The acute toxicity of estriol in animals is very low. Symptoms that may occur in the case of an acute oral overdosage are nausea, vomiting and possibly withdrawal bleeding in females. No specific antidote is known. If necessary a symptomatic treatment should be instituted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: natural and semisynthetic estrogens
ATC code: G03C A04

Mechanism of action
Ovestin Cream contains the natural female hormone estriol. Unlike other estrogens, estriol is short acting. It substitutes for the loss of oestrogen production. In case of vaginal atrophy, vaginally administered estriol induces the normalization of the urogenital epithelium and helps to restore the normal microflora and the physiological pH in the vagina.

Treatment of vaginal estrogen deficiency symptoms: Vaginally applied estrogen alleviates the symptoms of vaginal atrophy due to estrogen deficiency in postmenopausal women.

Clinical trial information

- Relief of vaginal symptoms was achieved during the first weeks of treatment.
- Vaginal bleeding after treatment with Ovestin has only rarely been reported.

5.2 Pharmacokinetic properties

Absorption
Intravaginal administration of estriol ensures optimal availability at the site of action. Estriol is also absorbed into the general circulation, as is shown by a sharp rise in the plasma levels of unconjugated estriol.

Distribution
Peak plasma levels are reached 1-2 hours after application. After vaginal application of 0.5 mg estriol, C_{max} is approximately 100 pg/ml, C_{min} is approximately 25 pg/ml and $C_{average}$ is approximately 70 pg/ml. After 3 weeks of daily administration of 0.5 mg vaginal estriol, $C_{average}$ has decreased to 40 pg/ml.

In a clinical trial, median plasma levels measured 12 hours after administration following 12 weeks of estriol cream administration were 8.5 pg/ml (interquartile range [IQR], 3.3-24.3). Following a median of 21 months (IQR, 9.2-38.4) of trice weekly administration, median serum oestriol levels in chronic group was 5.5 pg/ml (IQR, 1.9-10.2).

Biotransformation
Nearly all (90%) estriol is bound to albumin in the plasma, and in contrast with other estrogens, hardly any estriol is bound to sex hormone-binding globulin. The metabolism of estriol consists principally of conjugation and deconjugation during the enterohepatic circulation.

Elimination
Estriol, being a metabolic end product, is mainly excreted via the urine in the conjugated form. Only a small part (± 2%) is excreted via the faeces, mainly as unconjugated estriol.

5.3 Preclinical safety data

No particulars.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Octyldodecanol
Cetyl palmitate
Glycerol
Cetyl alcohol
Stearyl alcohol
Polysorbate 60
Sorbitan stearate
Lactic acid
Chlorhexidine dihydrochloride
Sodium hydroxide
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C. Do not freeze.

6.5 Nature and contents of container

Ovestin Cream is filled in collapsible aluminium tubes. The tubes are provided with a polyethylene screw cap. Ovestin Cream is available in tubes of 15g.

The CE-marked applicator consists of a styrene acrylonitrile copolymer barrel and a polyethylene plunger.

Each tube is packed, together with an applicator in a cardboard box.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Any unused medicinal product, the applicator or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA1691/017/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 August 1993

Date of last renewal: 23 August 2007

10 DATE OF REVISION OF THE TEXT

October 2020