SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ovestin 1 mg 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

Hormone replacement therapy (HRT) for the treatment of atrophy of the lower urogenital tract related to oestrogen deficiency.

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 2 to 3 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.

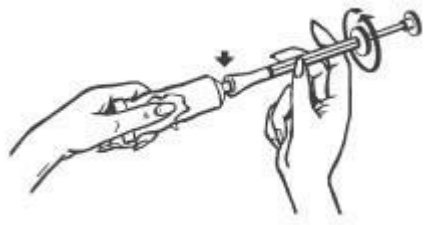
Ovestin Cream should be administered intravaginally by means of a calibrated applicator before retiring at night.

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

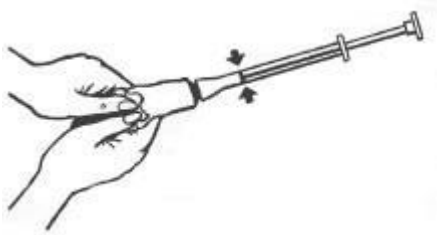
The following 'Instructions for Use' should be given to the patient and are included in the package leaflet:

Instructions for Use

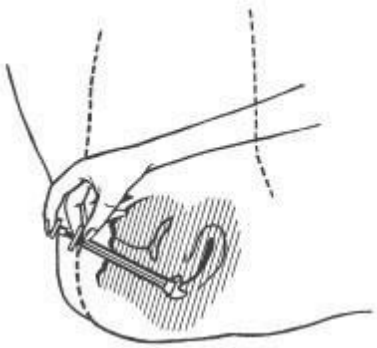
1. Remove the cap from the tube, invert it, and use the sharp point to open the tube.
2. Screw the end of the applicator onto the tube.



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.

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.

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

Cyclic administration of a progestagen to prevent endometrial stimulation is not necessary provided the daily dose does not exceed 1 applicator-dose (0.5 mg estriol) and this maximum dose is not used for more than several weeks (see section 4.4 Endometrial hyperplasia).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Pregnancy, suspected pregnancy, or in women breast feeding.
- 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
- 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.

<u>Medical examination/follow-up</u>

- Before initiation 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.

<u>Conditions which need supervision</u>

- 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

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

The endometrial safety of long term or repeated use of topical vaginal estrogens is uncertain. 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. Vaginal bleeding during medication should always be investigated. The patient should be informed to contact a doctor if vaginal bleeding occurs.

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.

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.

- The overall evidence suggests an increased risk of breast cancer in women taking combined estrogen-progestagen and possibly also estrogen-only HRT, that is dependent on the duration of taking HRT.
  Combined estrogen-progestagen therapy:
  - The randomised placebo-controlled trial the (Women's Health Initiative study (WHI), and epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined estrogen-progestagen for HRT that becomes apparent after about 3 years (see Section 4.8).

  Estrogen-only therapy:
  - The WHI trial found no increase in the risk of breast cancer in hysterectomised women using estrogen-only HRT. Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is substantially lower than that found in users of estrogen-progestagen combinations (see section 4.8).

  The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment.

- It is unknown whether Ovestin carries the same risk. 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. Long-term (at least 5-10 years) use of estrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer (see section 4.8). Some studies including the Women's Health Initiative (WHI) trial suggest that the long-term use of combined HRTs may confer a similar, or slightly smaller, risk (see Section 4.8). It is uncertain whether long-term use of low potency estrogens (such as Ovestin) confers a different risk than other estrogen only products.

Venous thromboembolism

- 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). These studies did not include Ovestin and, in the absence of data, it is unknown whether Ovestin carries the same risk.
- 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 (Body Mass Index >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 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)

There is no evidence from randomized controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined estrogen-progestagen or estrogen-only HRT.

Combined estrogen-progestagen therapy
The relative risk of CAD during use of combined estrogen-progestagen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD

due to estrogen-progestagen use is very low in healthy women close to menopause, but will rise with more advanced age.

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

Isachaemic stroke

- Combined estrogen-progestagen and 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).

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.)

Other conditions

- Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.
- Estriol is a weak gonadotrophin inhibitor without other significant effects on the endocrine system.
- 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).

4.5 Interaction with other medicinal products and other forms of interaction

No examples of interactions between Ovestin Cream and other medicines have been reported in clinical practice. 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.

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

- Estrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer. For further information see Sections "4.3 Contraindications" and "4.4 Special warnings and precautions for use"
- 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.

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined estrogen-progestagen therapy for more than 5 years.
- Any increased risk in users of estrogen-only therapy is substantially lower than that seen in users of estrogen-progestagen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

Million Women study– Estimated additional risk of breast cancer after 5 years' use

Age range (years)	Additional cases per 1000 never-users of HRT over a 5 year period*	Risk ratio#	Additional cases per 1000 HRT users over 5 years (95%CI)
Estrogen only HRT			
50-65	9-12	1.2	1-2 (0-3)
Combined estrogen-progestagen			
50-65	9-12	1.7	6 (5-7)

Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use.
* Taken from baseline incidence rates in developed countries.

US WHI studies - additional risk of breast cancer after 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users over 5 years (95%CI)
CEE estrogen-only			
50-79	21	0.8 (0.7-1.0)	-4 (-6-0)*
CEE + MPA estrogen-progestagen‡			
50-79	14	1.2 (1.0-1.5)	-4 (0-9)*

‡ When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.
* WHI study in women with no uterus, which did not show an increase in risk of breast cancer

- Ovarian cancer

Long-term use of estrogen-only and combined estrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer. In the Million Women Study 5 years of HRT resulted in 1 extra case per 2500 users.

- Risk of venous thromboembolism

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)
Oral combined estrogen-progestagen			
50-79	4	2.3 (1.2 - 4.3)	5 (1 - 13)

* Study in women with no uterus

Risk of coronary artery disease
The risk of coronary artery disease is slightly increased in users of combined estrogen-progestagen HRT over the age of 60 (see section 4.4).

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%Cl	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.

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 since it has only a short retention time in the nuclei of endometrial cells. It substitutes for the loss of oestrogen production in menopausal women and alleviates menopausal symptoms. Estriol is particularly effective in the treatment of urogenital symptoms. In case of atrophy of the lower urogenital tract estriol induces the normalization of the urogenital epithelium and helps to restore the normal microflora and the physiological pH in the vagina. As a result, it increases the resistance of the urogenital epithelial cells to infection and inflammation.

Clinical trial information
- Relief of menopausal 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.

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 ($\pm$ 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 25ºC. 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

February 2017