# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Ovesse 1 mg/g vaginal cream

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1mg estriol in 1g cream

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Vaginal cream

Homogeneous, smooth, white to nearly white mass of creamy consistency.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of vaginal atrophy due to oestrogen deficiency in postmenopausal women aged 50 years and above who have not had a period for at least 1 year.

### 4.2 Posology and method of administration

Ovesse vaginal cream is a local oestrogen-only product for intravaginal use.

Ovesse may be used in women with or without an intact uterus.

Initial dose: One application (0.5mg estriol in 0.5g of cream) per day for two weeks.
Maintenance dose: One application twice a week.

Restarting treatment: For patients still experiencing symptom relief after a break from therapy, it is recommended that treatment is restarted at the maintenance dose. For patients experiencing bothersome symptoms again after a break from therapy, it is recommended to restart treatment at the initial daily dose regimen for 2 weeks, followed by the maintenance twice weekly dose.

Switching from other local vaginal oestrogen preparations: Patients experiencing symptom relief from vaginal oestrogen preparations that are being used at the recommended dose can be switched to the maintenance dose of Ovesse vaginal cream

provided:

• The woman has used her current vaginal oestrogen product for more than 3 months, and;
• Her symptoms are adequately controlled, and;
• Her health status is unchanged since her last prescription.

Treatment with Ovesse cream may be started on any day.

Treatment should be continued for as long as needed and symptoms often return if treatment is stopped.

A missed dose should be administered as soon as remembered. However, two doses should not be administered on the same day.

*Route of Administration*
Ovesse vaginal cream is administered intravaginally by means of a calibrated applicator. One applicator-dose (applicator filled to the red mark) is 0.5g Ovesse vaginal cream containing 0.5 mg estriol.

The following 'Instructions for Use' should be given to the patient and are included in the Patient Information Leaflet:

<u>How to apply the cream</u>
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 red ring marked on the body. Fill the applicator up to the ring mark with Ovesse vaginal cream to get the correct dose.

1. Remove the cap from the tube and turn it upside down. Then use the sharp point 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 ring mark).
4. Unscrew applicator from the tube and put the cap back on the tube.
5. To apply the cream, lie down, put the end of the applicator deep into the vagina and slowly push plunger all the way in.

<u>Cleaning the applicator</u>
After use, pull the plunger out of the barrel. Wash the plunger and barrel in hand hot, soapy water. Do not use detergents. Rinse well with clean water afterwards.
DO NOT PUT THE APPLICATOR IN BOILING WATER.

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

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

*Children*
There are no clinical trials to support the use in children.

## 4.3 Contraindications

- Known Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- **Known, past or suspected endometrial cancer**
- **Undiagnosed genital bleeding**
- **Untreated endometrial hyperplasia**
- **Women with an intact uterus who have previously been treated with unopposed systemic oestrogens**
- **Vulval dermatoses**
- **Current vaginal infection prior to starting treatment**
- **Vulval rash**
- **Severe vaginal itching**
- Known, past or suspected oestrogen-dependent malignant tumors (e.g. breast cancer, ovarian cancer)
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction, ischaemic stroke)
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4)
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal
- Porphyria

## 4.4 Special warnings and precautions for use

Treatment initiation or restarting and medical examination

For the treatment of postmenopausal symptoms, HRT should only be initiated or reinstituted for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at every pharmacy visit for resupply and HRT should only be continued as long as the benefit outweighs the risk. **Continued suitability of treatment with Ovesse vaginal cream should be verified at each supply.**

Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Women should be referred to their doctor before or at any time during treatment if this, or the contraindications and warnings for use, indicate a need for a physical (including pelvic and breast) examination by a doctor.

Women should be advised to report any unexpected vaginal bleeding to their doctor
or nurse.

Women should be advised what changes in their breasts 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 requiring a doctor referral before treatment initiation

- Women receiving hormonal therapy, including systemic HRT, unless she has previously received a prescription for a concurrent vaginal oestrogen product and her health status is unchanged since her last prescription.

- Women with a history of:

  - Endometriosis (see below) unless:

    - She has previously received a prescription for vaginal oestrogens and her health status is unchanged since her last prescription, and

    - she has no recent symptoms of endometriosis ;

  - Endometrial hyperplasia (see below) unless:

    - She has previously received a prescription for vaginal oestrogens and her health status is unchanged since her last prescription, or

    - she has had a hysterectomy.

- Women switching to Ovesse from another vaginal oestrogen product who have:
  - Used their current vaginal oestrogen product for less than 3 months, or;
  - Been using their vaginal oestrogen product at the recommended dose and are experiencing bothersome symptoms

Follow-up

Women with symptoms that do not start to improve or worsen after 3 months of treatment, should be referred to their doctor.
The dose of Ovesse should not be increased.
If Ovesse does not relieve symptoms adequately, advice from a doctor should be sought.

**Women should be advised that symptoms often recur when the treatment is stopped**

Reasons for immediate withdrawal of therapy:

Therapy should be discontinued, and advice sought from a doctor in case a

contraindication is identified or if the following situations occur or recur during treatment:

- New onset of vaginal bleeding or spotting
- New onset of vaginal itching
- Vaginal infection not adequately treated by a pharmacy treatment
- Symptoms of endometriosis

Prompt advice should also be sought from a doctor 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

- Women with an intact uterus with abnormal bleeding of unknown aetiology or women with an intact uterus who have previously been treated with unopposed oestrogens should be examined with special care in order to exclude hyperstimulation/malignancy of the endometrium. Therefore use of vaginal oestrogens in these women should remain under the supervision of a doctor.

- 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 Ovesse vaginal cream, the systemic exposure of estriol remains within the normal postmenopausal range when it is 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 oestrogens is uncertain. Therefore, if repeated, treatment should be reviewed at least annually, with special consideration given to any symptoms of endometrial hyperplasia or carcinoma.

- 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 woman should be advised to contact her doctor in case bleeding or spotting occurs during treatment with Ovesse vaginal Cream.

- In order to prevent endometrial stimulation, each dose should not exceed 1 application (0.5 mg estriol). Also, the dosing schedule in section 4.2 must not be exceeded. 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.

***The following risks have been associated with <u>systemic</u> HRT and apply to a lesser extent for Ovesse vaginal cream of which the systemic exposure to estriol remains within the normal postmenopausal range when used in a twice weekly administration.*** However, being an HRT product, the following need to be considered in case of long term or repeated use of this product.

<u>Conditions that may be aggravated during exposure to oestrogen</u>

The following conditions may recur or be aggravated during oestrogen treatment. 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 advised to inform their doctor that they are using Ovesse and seek advice from a doctor if they recur or are aggravated during treatment:

- Leiomyoma (uterine fibroids)
- Risk factors for thromboembolic disorders (see below)
- Risk factors for oestrogen 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.
- Epilepsy
- Asthma
- Otosclerosis

<u>Breast cancer</u>

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.

<u>Ovarian cancer</u>

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.

<u>Venous thromboembolism</u>

- **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 recognised risk factors for VTE include, use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m2), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE.

  As in all postoperative patients, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilisation 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.

- 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 counseling 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 therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (eg, painful swelling of a leg, sudden pain in the chest, dyspnea).

Coronary artery disease (CAD)

*Oestrogen-only*
Randomized controlled data found no increased risk of CAD in hysterectomized women using **systemic oestrogen-only therapy.**

Ischemic stroke

**Systemic** oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischemic 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

Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients in Ovesse Vaginal Cream is increased.

Women with pre-existing hypertriglyceridemia 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.

Exogenous oestrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

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 of increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65.

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

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.

## 4.5 Interaction with other medicinal products and other forms of interaction

Due to the vaginal administration and minimal systemic absorption, it is unlikely that any clinically relevant drug interactions will occur with Ovesse. However interactions with other locally applied vaginal treatments should be considered.

## 4.6 Fertility, pregnancy and lactation

Ovesse is not indicated during pregnancy. If pregnancy occurs during medication with Ovesse treatment should be withdrawn immediately. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to oestrogens indicate no teratogenic or

foetotoxic effects.
Ovesse is not indicated during lactation.

## 4.7 Effects on ability to drive and use machines

As far as is known Ovesse has no effect on alertness and concentration.

## 4.8 Undesirable effects

The following adverse reactions, associated with estrogen treatment may occur during estriol therapy or overdose: Nausea and vomiting, breast tenderness or pain in the breasts, vaginal bleeding or spotting during or on withdrawal of therapy, excessive production of cervical mucus, headache.

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

Tabulated list of adverse reactions
The following convention has been utilised for the classification of frequency: Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

| System organ class | Frequency | Adverse reactions* |
|---|---|---|
| **General disorders and administration site conditions** | Not Known | Application site irritation and pruritus<br>Influenza-like illness |
| **Renal and urinary disorders** | Not Known | Dysuria |
| **Reproductive system and breast disorders** | Not Known | Breast discomfort and pain, Genital burning sensation, Vulvovaginal burning sensation |

*MedDRA version 28.0
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 Estriol 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 (yrs) | Incidence per 1000 women in placebo arm over 5 years | Risk ratio & 95%CI | Additional cases per 1000 HRT users |
|---|---|---|---|
| ***Oral estrogen-only*** | | | |
| *50-59* | **7** | *1.2 (0.6 – 2.4)* | *1 (-3 – 10)* |

* Study in women with no uterus

**Risk of ischaemic stroke**

- The use of **systemic** HRT 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 ischaemic stroke* 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 over 5 years |
|---|---|---|---|
| 50-59 | 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 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).

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 Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

### 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 oestrogens ATC code: G03CA04

Mechanism of action
Ovesse contains the natural female hormone estriol. Unlike other oestrogens, estriol is short acting. It substitutes for the loss of oestrogen production.

In cases of vaginal atrophy, vaginally administered estriol induces normalisation of the vaginal epithelium and thus helps to restore the normal microflora and a physiological pH in the vagina.

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

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

### 5.2 Pharmacokinetic properties

Absorption
After administration of Ovesse Cream, estriol is also absorbed from the vagina into the general circulation, shown by a sharp rise in plasma estriol, followed by a gradual decline.

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 estriol 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 oestrogens, 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 feces, mainly as unconjugated estriol.

### 5.3 Preclinical safety data

No particulars.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Octyldodecanol; cetyl palmitate; glycerin; cetyl alcohol; stearyl alcohol; Polysorbate 60; sorbitan stearate; chlorhexidine hydrochloride; lactic acid; sodium hydroxide to pH 4, purified water.

### 6.2 Incompatibilities

None stated.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Do not store above 25˚C. Do not freeze.

### 6.5 Nature and contents of container

15g collapsible aluminium tube with styrene acrylonitrile (copolymer) applicator.

### 6.6 Special precautions for disposal

Please see Section 4.2

## 7 MARKETING AUTHORISATION HOLDER

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

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 39699/0118

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/03/2024

## 10 DATE OF REVISION OF THE TEXT

19/05/2026