SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Estriol 1mg/g 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 oestrogen deficiency symptoms:**
  - Treatment of symptoms of vaginal atrophy due to oestrogen deficiency in postmenopausal women.

- As pre-surgery therapy for vaginal operations and during subsequent convalescence.

4.2 Posology and method of administration

Estriol 1mg/g cream is an estrogen-only product for intravaginal use.

Adults and Elderly

- Treatment of atrophic vaginitis

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.

- Pre-surgery therapy
  One applicator-dose per day should begin 2 weeks before the operation.

- Post-surgery therapy
  Following surgery a period of at least 2 weeks should be allowed before resuming therapy using one applicator-dose twice a week.

A missed dose should be administered as soon as remembered, unless it is more than 12 hours overdue. In the latter case the missed dose should be skipped and the next dose should be administered at the normal time. Two doses should never be administered on the same day.

Route of Administration

Estriol 1mg/g cream is administered intravaginally by means of a calibrated applicator.
One applicator-dose (applicator filled to the red mark) is 0.5g Estriol 1mg/g 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:

How to Apply the Cream

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

The applicator has a ring marked on the body. Fill the applicator up to the ring mark with Estriol 1mg/g 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.

Cleaning the applicator

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 Estriol 1mg/g cream 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 another continuous combined HRT product, treatment with Estriol 1mg/g cream may be started on any day. Women who switch from cyclic HRT regimen should start Estriol 1mg/g cream treatment one week after completion of the cycle.

Children

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

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, pulmonaryembolism);
- 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 have failed to return to normal;
- Known 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 favorable 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 breasts should be reported to their doctor or nurse (see “Breast cancer” below). Investigations, including mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

In case of vaginal infections, these should be treated before therapy with Estriol 1mg/g cream is started.

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 Estriol 1mg/g cream, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- A history of, or 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

- 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 Estriol 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 estrogens is uncertain. Therefore, if repeated, treatment should be reviewed at least annually.

- Unopposed estrogen stimulation may lead to premalignant 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.

- 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 several weeks (**maximum 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.

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 within the normal postmenopausal range when used in a twice weekly administration. However, they should be considered in case of long term or repeated use of this product.

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, especially estrogen-progestagen combined treatment, increases the density of mammographic images which may adversely affect 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 Estriol 1mg/g cream carries the same risk. In a 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 higher 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 HRT than later.
- 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 a personal history or family history, severe obesity (BMI > 30 kg/m^2) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.
- As in all postoperative patients, prophylactic measures need to 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

- Estrogens 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 Estriol 1mg/g cream is increased.
- Women with pre-existing hypertriglyceridemia should be followed closely during estrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen 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 estrogen-only HRT after the age of 65.
- Estriol 1mg/g 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 interaction

Due to the vaginal administration and minimal systemic absorption, it is unlikely that any clinically relevant drug interactions will occur with Estriol 1mg/g cream. However interactions with other locally applied vaginal treatments should be considered.
The following interactions have been described with use of combined oral contraceptives which may also be relevant for Estriol 1mg/g cream. 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. hydantoins, barbituates, carbamezapin), anti-infectives (e.g. griseofulvin, rifamycins, the antiretroviral agents nevirapine and efavirenz) and herbal preparations containing St John's wort (Hypericum Perforatum). Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones.

Clinically, an increased metabolism of estrogens may lead to decreased effectiveness of Estriol 1mg/g cream and changes in uterine bleeding profile.

Estriol may possibly increase the pharmacological effects of corticosteroids, succinylcholine, theophyllines and troleandomycin.

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

Estriol 1mg/g cream is not indicated during pregnancy. If pregnancy occurs during medication with Estriol 1mg/g cream treatment should be withdrawn immediately.

The results of most epidemiological studies to date relevant to inadvertent foetal exposure to estrogens indicate no teratogenic or foetotoxic effects.

Estriol 1mg/g cream is not indicated during lactation.
Estriol is excreted in breast milk and may decrease milk production.

4.7 Effects on ability to drive and use machines

As far as is known Estriol 1mg/g cream 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 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 estrogens
ATC code: G03CA04

Mechanism of action
Estriol 1mg/g cream contains the natural female hormone estriol. Unlike other estrogens, estriol is short acting. It substitutes for the loss of estrogen 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 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 Estriol 1mg/g cream has only rarely been reported

5.2 Pharmacokinetic properties

Absorption

After administration of Estriol 1mg/g 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 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 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 39699/0058

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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