SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ESTRIOL 0.01% w/w Cream

GYNEST 0.01% w/w Cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Estriol 0.01% w/w

Excipients: Arachis oil and Benzoic acid

For a full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Vaginal Cream.

Description of the product:

Estriol Cream is a whitish cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Hormone replacement therapy for treatment of atrophic vaginitis and kraurosis in post-menopausal women.
2. Treatment of pruritus vulvae and dyspareunia associated with atrophic vaginal epithelium.

4.2 Posology and method of administration

Gynest Cream is an oestrogen-only product for intravaginal use.

No progestogen needs to be added (but please refer to section 4.4).

Guidance on how to start therapy and maintenance

Gynest Cream can be started any time after the manifestation of atrophic vaginitis or associated symptoms (eg dyspareunia, pruritus).

The recommended initial daily dose is one applicator full per day.

A maintenance dose of one applicator full twice a week may be used after restoration of the vaginal mucosa has been achieved.

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. Attempts to discontinue medication should be made at three to six month intervals following physical examination.

Missed Dose: When a dose is inadvertently forgotten, resume dosing when the omission is realized.

Administration:

Gynest Cream is to be applied into the vagina, using an applicator. The applicator holds 5ml of cream containing 0.5mg estriol. The filled applicator should be inserted high into the vagina and emptied, preferably in the evening.

Remove the cap from a new tube and use the top of the cap to pierce the metal seal on the tube.

One end of the applicator is fitted with a plunger. Ensure the plunger is fully inserted into the applicator. Screw the other end of the applicator onto the tube. Squeeze the tube, so that the barrel of the applicator fills with cream. Unscrew the applicator and replace the cap on the tube.

Lie down, with knees bent and spread apart. Gently insert the open end of the applicator well into the vagina. Push the plunger firmly but gently as far as it will go to empty the cream into the vagina.

Keeping the plunger pressed down firmly, grip the applicator by the barrel and remove it.

There is no relevant indication for use of Gynest in children

4.3 Contra-indications

- Known hypersensitivity to estriol or any of the excipients.
- Known, past or suspected cancer of the breast
- Known or suspected oestrogen-dependent malignant tumours (eg endometrial cancer)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Known thrombophilic disorders (eg protein C, protein S, or antithrombin deficiency, see section 4.4)
- Active or recent arterial thromboembolic disease (eg angina, myocardial infarction)
- 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

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.

Gynest Cream contains arachis oil (peanut oil) and should not be applied by patients known to be allergic to peanuts (see Section 4.3). As there is a possible relationship between allergy to peanuts and allergy to soya, patients with soya allergy should also avoid Gynest Cream.

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 contra-indications 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 appropriate imaging tools eg 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 Gynest Cream, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for oestrogen dependent tumours, eg 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (eg 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 oestrogens are administered alone for prolonged periods of time. The reported increase in endometrial cancer risk among oestrogen-only users varies from 2 to12-fold greater compared with non-users, depending on the duration of treatment and oestrogen dose (see section 4.8). After stopping treatment risk may remain elevated for at least 10 years.

The addition of a progestogen cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestogen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.

The endometrial safety of long-term or repeated use of topical vaginal oestrogens is uncertain. Therefore, if repeated, treatment should be reviewed at least annually, with a special consideration given to any symptoms of endometrial hyperplasia or carcinoma.

Break-through bleeding and spotting may occur during the first months of treatment. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestogens to oestrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis, if they are known to have residual endometriosis.

The following risks have been associated with systemic HRT and apply to a lesser extent for oestrogen products for vaginal application of which the systemic exposure to the oestrogen remains **within** the normal postmenopausal range. 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.

Combined oestrogen-progestogen therapy

- The randomised placebo-controlled trial the Women's Health Initiative study (WHI), and a meta-analysis of prospective epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestogen for HRT that becomes apparent after about 3 (1-4) years (see Section 4.8)

Oestrogen-only therapy

- The Women's Health Initiative (WHI) trial found no increase in the risk of breast cancer in hysterectomised women using oestrogen-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 oestrogen-progestogen combinations (see Section 4.8).

HRT, especially oestrogen-progestogen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Ovarian cancer

Ovarian cancer is much rarer than breast cancer. Long-term (at least 5-10 years) use of oestrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer (see section 4.8). Some studies including the WHI trial suggest that the long-term use of combined HRT may confer a similar, or slightly smaller, risk (see section 4.8).

Venous thromboembolism

- HRT is associated with a 1.3 to 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/m^2), 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 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' (eg 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, dyspnoea).

Coronary artery disease (CAD)

- There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestogen or oestrogen-only HRT.
- Combined oestrogen-progestogen therapy

  The relative risk of CAD during use of combined oestrogen+progestogen 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 oestrogen+progestogen use is very low in healthy women close to menopause, but will rise with more advanced age.
- Oestrogen-only therapy

  Randomised controlled data found no increase of CAD in hysterectomised women using oestrogen-only therapy.

Ischaemic Stroke

- Combined oestrogen-progestogen and oestrogen-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

- Oestrogens 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 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-l-antitrypsin, ceruloplasmin).

  With vaginal administration, stimulation of the liver by the first-pass effect is avoided and thus, transvaginal oestrogens might affect hormone binding proteins and other serum proteins produced by the liver less than oral hormones.
- 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.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of oestrogens may be increased by concomitant use of substances known to induce drug metabolising enzymes, specifically CYP 450 enzymes, such as anticonvulsants (eg phenobarbital, phenytoin, carbamazepine) and anti-infectives (eg rifampicin, rifabutin, nevirapine, efavirenz) and also bosentan.

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St. John's Wort (*Hypericum perforatum*) may induce the metabolism of oestrogens. With intravaginal administration, the first-pass effect in the liver is avoided and thus, estriol given intravaginally might be less affected by enzyme inducers than oral hormones.

Clinically, an increased metabolism of oestrogens may lead to decreased effect and changes in the uterine bleeding profile.

Contact between contraceptive diaphragms or condoms and the cream must be avoided since the rubber may be damaged by this preparation.

Oestrogen-containing oral contraceptives have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. Although the potential interaction between oestrogen-containing hormone replacement therapy and lamotrigine has not been studied, it is expected that a similar interaction exists, which may lead to a reduction in seizure control

among women taking both drugs together. Therefore, dose adjustment of lamotrigine may be necessary.

4.6 Pregnancy and lactation

Pregnancy

Gynest Cream is not indicated during pregnancy. If pregnancy occurs during use of Gynest Cream, 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 effect.

Lactation

Gynest Cream is not indicated during lactation.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

No undesirable effects were reported in two open, uncontrolled clinical trials of short duration involving 47 women.

However, in a double-blind, placebo controlled clinical trial of 30 women treated with Gynest, the following undesirable effects were reported in the estriol pessary treatment group more frequently than in the placebo group:

Breast pain, micturition frequency increased, vaginal discharge, cystitis, leg pain, pre-menstrual tension, lower abdominal pain, palpitations and depression.

Class effects associated with systemic HRT

The following risks have been associated with systemic HRT and apply to a lesser extent for oestrogen products for vaginal application of which the systemic exposure to oestrogen remains within the normal postmenopausal range.

Endometrial cancer risk

Postmenopausal women with a uterus

The endometrial cancer risk is about 5 in every 1000 women with a uterus not using HRT.

In women with a uterus, use of oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4).

Depending on the duration of oestrogen-only use and oestrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1000 women between the ages of 50 and 65.

Adding a progestogen to oestrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study the use of five years of combined (sequential or continuous) HRT did not increase risk of endometrial cancer (RR of 1.0 (0.8-1.2)).

Ovarian cancer

Long-term use of oestrogen-only and combined oestrogen-progestogen 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 HRT (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 oestrogen-only*			
50-59	7	1.2 (0.6 – 2.4)	1 (-3 –10)*
Oral combined oestrogen-progestogen			
50-59	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 oestrogen-progestogen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke

. The use of oestrogen-only and oestrogen + progestogen 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 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
50-59	8	1.3 (1.1 – 1.6)	3 (1-5)
*No differentiation was made between ischaemic and haemorrhagic stroke			

Other adverse events which have been reported in association with oestrogen/progestogen treatment are:

- Gall bladder disease.
- Skin and subcutaneous tissue 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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of overdose of oestrogen therapy may include breast pain or tenderness, nausea, break-through bleeding, abdominal cramps and/or bloating. Vaginal lavage should be considered. If accidental ingestion of large quantities of the product occurs, an appropriate method of gastric emptying may be considered.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural and semisynthetic oestrogens, plain; ATC Code: G03CA04

The active ingredient, synthetic estriol, is chemically and biologically identical to endogenous human estriol. It substitutes for the loss of oestrogen production in menopausal women and alleviates menopausal symptoms.

Estriol, a weak oestrogen, is a natural metabolite of estradiol, the predominant oestrogen. Estriol exerts estrogenicity by binding to oestrogen receptors, present in the female genital tract. Estriol, oral or vaginal, similar to estradiol, corrects lowered proliferation and abnormal physiology in the atrophic vaginal epithelium seen in oestrogen deficient states, such as after natural or surgical menopause. In contrast, the histology of the endometrium after using Gynest Cream rarely shows minor signs of proliferation in previously atrophic endometria.

Clinical trial information

Improvement of vaginal epithelial cytology was noted in 47 subjects with vaginal atrophy in two clinical trials with daily administration of Gynest Cream after 2 weeks in one trial and after 4 weeks in the other trial.

5.2 Pharmacokinetic properties

Estriol is readily absorbed following intravaginal application. Peak serum estriol concentrations are generally observed within 2 hours following intravaginal application and remain elevated for 6 hours. Systemic bioavailability on vaginal administration is better than after oral administration. Intravaginal application of 1 mg estriol in women with senile atrophy of the vaginal epithelium results in serum levels similar to those seen after oral administration of 10 mg estriol.

Plasma estriol levels increased from <90pmol/L (26 pg/mL) about fifty fold over a few hours after intravaginal administration of Estriol Cream. Eight to ten hours after administration, 50% of women still had estriol levels above 90pmol/L (26 pg/mL).

Estriol circulates with the blood, about 14% free, 8% bound to SHBG and the rest bound to albumin. Primary metabolites of estriol include the 16-alpha-glucuronide, 3-glucuronide, 3-sulfate and 3-sulfate 16-alpha-glucuronide. More than 95% of estriol is excreted in the urine, predominantly in the form of glucuronides.

5.3 Preclinical safety data

No relevant information additional to that contained elsewhere in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzoic acid

Arachis oil

Glyceryl monostearate

Glycerin

Glutamic acid

Purified water

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Aluminium tube with screw cap containing 80 g [or 78g]* cream supplied with a single reusable applicator* or 16 disposable plastic vaginal applicators.

* not currently marketed.

6.6 Special precautions for disposal

Please refer to Section 4.2 Posology and Method of Administration.

After each use, clean the applicator:

Pull the plunger from the barrel with a sharp tug. Clean barrel and plunger with mild soap and warm (not boiling) water. Rinse well. Reinsert the plunger into the barrel for next use.

A replacement applicator (the Gynest Vaginal Applicator) can be obtained at pharmacies.

Empty tubes may be disposed of in household waste. Return tubes with drug remaining to your pharmacy for destruction. Do not dispose of unused drug in household waste or flush it down the toilet.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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