SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Estriol 0.5 mg/g vaginal cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g vaginal cream contains 0.5 mg estriol.

Excipient(s) with known effect
1 g vaginal cream contains 50 mg cetostearyl alcohol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Vaginal cream

White cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of symptoms of vaginal atrophy due to oestrogen deficiency in postmenopausal women.

4.2 Posology and method of administration

Posology
Postmenopausal women
In general, the recommended dose during the first three weeks of treatment is 1 g (equivalent to 0.5 mg of estriol) per day with an applicator.
Thereafter, a maintenance dose of one applicator filling of 1 g (corresponding to 0.5 mg estriol) should be used twice a week.

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 oestrogen products for vaginal application of which the systemic exposure to the oestrogen remains within the normal postmenopausal range, it is not recommended to add a progestagen (see section 4.4).

Estriol 0.5 mg/g vaginal cream is not a contraceptive.

Paediatric population
There is no relevant use of Estriol 0.5 mg/g vaginal cream in the paediatric population.

Missed dose
In case of daily use during the first weeks of treatment
If the missed dose is noticed on the following day, it should not be made up. In that case, the usual dosing schedule should be resumed.

In case of 2 applications per week
The missed dose should be administered as soon as possible.

Method of administration
Vaginal use.

Estriol 0.5 mg/g vaginal cream should ideally be applied in the evening before going to bed by inserting the applicator deep into the vagina.

4.3 Contraindications

- Known, past or suspected breast cancer.
- Known or suspected oestrogen-dependent malignant tumours (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 have failed to return to normal.
- Porphyria.
- Known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

- For the treatment of postmenopausal symptoms, hormone replacement therapy (HRT) should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually, and HRT should only be continued as long as the benefit outweighs the risk.

- Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

Medical examination/follow-up

- Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see section "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.

  Vaginal infections should be treated prior to initiating therapy with Estriol 0.5 mg/g vaginal cream.

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 0.5 mg/g vaginal cream, in particular:

  – Leiomyoma (uterine fibroids) or endometriosis
  – 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
  – A history of endometrial hyperplasia (see below)
  – Epilepsy

– Asthma
– Otosclerosis

Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contraindication is discovered and in the following situations:

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

Endometrial hyperplasia and carcinoma

- In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when systemic oestrogens are administered alone for prolonged periods.
- For oestrogen products for vaginal application of which the systemic exposure to oestrogen remains within the normal postmenopausal range, it is not recommended to add a progestogen.
- Endometrial safety of long-term (more than one year) or repeated use of local vaginally administered oestrogen is uncertain. Therefore, if repeated, treatment should be reviewed at least annually.
- Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, caution is advised when using this product in women who have undergone hysterectomy because of endometriosis, especially if they are known to have residual endometriosis.
- If bleeding or spotting appears at any time during 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 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 medicinal 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 using low-dose vaginally applied oestrogen. It is unknown if low-dose vaginal oestrogens stimulate recurrence of breast cancer.

HRT, especially oestrogen-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 oestrogens. It is unknown whether this medicine carries the same risk. In several population-based control-studies, estriol was found not to be associated with an increased risk of breast cancer, in contrast to other oestrogens. 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 using oestrogen-only **systemic** HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.

Venous thromboembolism

- **Systemic** HRT is associated with a 1.3 - 3-fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see section 4.8).

- Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).

- Generally 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 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 a 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 (see section 4.3).

- Women already on chronic anticoagulant treatment require careful consideration of the benefit/risk balance of use of HRT.

- If VTE develops after initiating HRT, the medicinal product 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, dyspnoea).

Coronary artery disease (CAD)

Oestrogen-only
Randomised controlled studies found no increased risk of CAD in hysterectomised women using **systemic** oestrogen-only therapy.

Ischaemic stroke

Systemic oestrogen-only therapy is 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. Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients in Estriol 0.5 mg/g vaginal cream is increased.

- Women with pre-existing hypertriglyceridaemia should be followed closely during oestrogen replacement or HRT, 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 the concentration of 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 biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-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.

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 oestrogens other than ethinyl estradiol, such as estradiol, estriol and conjugated oestrogens had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of subjects taking these other oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir hydrate/paritaprevir hydrate/ritonavir with or without dasabuvir (see section 4.5).

Excipients

Cetostearyl alcohol may cause local skin reactions (e.g. contact dermatitis). If irritation of the skin and mucous membranes occurs, use should be less frequently or discontinued. No specific countermeasures are required.

Use with latex condoms

When simultaneously using condoms made of latex it should be considered that the fats and emulsifiers contained in Estriol 0.5 mg/g vaginal cream may lead to a reduction in tensile strength and thus impair the safety of condoms.

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 0.5 mg/g vaginal cream. However, interactions with other locally applied vaginal treatments should be considered.

The following interactions may be described with use of oral contraceptives, which may also be relevant for this medicine.

The metabolism of oestrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepin) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit indicing properties when used concomitantly with steroid hormones.

Herbal preparations containing St. John's Wort (Hypericum Perforatum) may induce the metabolism of oestrogens.

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

Estriol may possibly increase the pharmacological effects of corticosteroids, succinylcholine, theophylline 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 oestrogens other than ethinyl estradiol, such as estradiol, estriol and conjugated oestrogens had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of subjects taking these other oestrogens, 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

Pregnancy
Estriol 0.5 mg/g vaginal cream is not indicated during pregnancy. If pregnancy occurs during medication with Estriol 0.5 mg/g vaginal 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 effects.

Breast-feeding
Estriol 0.5 mg/g vaginal cream is not indicated during breast-feeding.

4.7 Effects on ability to drive and use machines

As far as known, Estriol 0.5 mg/g vaginal cream does not affect the ability to drive or use machines.

4.8 Undesirable effects

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), and not known (cannot be estimated from the available data).

System organ class	**Uncommon**	**Rare**	**Very rare**
Reproductive system and breast disorders	Mastodynia (during the first weeks of treatment), a feeling of heat or itching in the vagina (at the start of treatment)	Uterine bleeding (even after discontinuation)	
General disorders and administration site conditions	Weight gain due to fluid retention	(Migraine-type) headaches	
Vascular disorders	Increased blood pressure		
Gastrointestinal disorders	Nausea or other gastrointestinal symptoms		
Musculoskeletal and connective tissue disorders			Leg cramps or "heavy legs"
Skin and subcutaneous tissue disorders			Allergic skin reactions (with itching, redness, swelling)

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.

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 2 000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2 000 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 HRT (see section 4.4). Results of the WHI studies are presented in the following table:

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

Age range (years)	Incidence per 1 000 women in placebo arm over 5 years	Risk ratio and 95 % CI	Additional cases per 1 000 HRT users
Oral oestrogen-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). Results of the WHI studies are presented in the following table:

WHI studies combined – Additional risk of ischaemic stroke* over 5 years' use

Age range (years)	Incidence per 1 000 women in placebo arm over 5 years	Risk ratio and 95 % CI	Additional cases per 1 000 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 systemic oestrogen/progestagen treatment:

- Gallbladder 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 the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Symptoms of an overdose include nausea, vomiting, feeling of tightness in the breasts and vaginal bleeding.

Management
The symptoms can be eliminated by reducing the dose or discontinuing treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Oestrogens, ATC code: G03CA04

The active substance, synthetic estriol, is chemically and biologically identical to endogenous human estriol.

When applied locally, estriol reduces discomfort in the vaginal area caused by oestrogen deficiency. In the vaginal area, intermediate and increasingly superficial cells are primarily seen instead of atrophic cell formation; inflammatory changes recede and the reappearance of Döderlein flora is promoted.

Clinical trial information
- Relief of oestrogen-deficiency symptoms
- Relief of vaginal symptoms was achieved during the first few weeks of treatment.

5.2 Pharmacokinetic properties

The therapeutic efficacy of Estriol 0.5 mg/g vaginal cream requires local availability of the active substance at the site of application. Since systemic absorption occurs, the following information is given here:

Absorption

After vaginal application of 0.5 mg estriol a mean maximum estriol serum concentration (C_{max}) of 144.2 pg/ml estriol is reached after 2 h on average.

Distribution
Estriol is present in plasma in 8 % free form, 91 % is bound to albumins and 1 % to SHBG.

Biotransformation
Metabolisation in the liver leads primarily to glucuronides and sulphates.

Elimination
The plasma half-life ($T_{1/2}$) of the unconjugated estriol is 9 - 10 hours. After 4 hours, up to 90 % is present in an ineffective conjugated form.

Estriol is eliminated mainly renally in the form of conjugates and to a small extent via the bile.

5.3 Preclinical safety data

Due to the marked differences between the different species of laboratory animals and in relation to humans, laboratory test results with animals involving the use of oestrogen have only limited predictive value for use in humans.

Animal studies have shown that estriol and other oestrogens have an embryolethal effect after systemic administration, even at relatively low doses. Malformations of the urogenital tract and feminisation of male foetuses have been observed.

No preclinical data on the vaginal application of estriol are available.

Preclinical data from conventional studies on chronic toxicity, genotoxicity and carcinogenic potential have not demonstrated any special risks for humans, other than the risks already described in other sections of this summary of product characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cetostearyl alcohol
Macrogol 20 glycerol monostearate
Glycerol monostearate (E471)
Isopropyl myristate
Carbomer
Sodium hydroxide (E524)

Purified water
Phenoxyethanol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

Shelf life after first opening: 1 year (30 g tube), 3 years (50 g and 100 g tube)

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium tubes of 30 g (physician sample), 30 g, 50 g and 100 g cream plus applicator. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

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