SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Estriol DR. KADE 0,03 mg ovules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 pessary contains 0.03 mg estriol.

Excipient with known effect:
Each pessary contains a maximum of 0.008 mg butylhydroxytoluene.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pessary

White, homogenous pessaries.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Local treatment of vaginal symptoms of estrogen deficiency in postmenopausal women.

4.2 Posology and method of administration

Posology

During the first 3 weeks of treatment one pessary is administered daily. Thereafter a maintenance dose of 1 pessary twice a week is recommended.

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

For estrogen products for vaginal application of which the systemic exposure to the estrogen is very low, it is not recommended to add a progestagen (but see section 4.4).

Method of administration

The pessary should be introduced deeply into the vagina, preferably in the evening before going to bed.

Missed dose

- During daily use within the first 3 weeks of treatment:
  If a missed dose is not realized before the next day, it should not be replaced. In that case the usual dosing schedule should be resumed.

- During twice-weekly use:
  If the administration of the medicinal product has been forgotten at a scheduled date during the twice-weekly maintenance treatment, the missed dose should be administered as soon as possible.

4.3 Contraindications

– Known, past or suspected breast cancer;
– Known or suspected estrogen-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;
– 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, 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.

<Invented name> must not be combined with estrogen preparations for systemic treatment, as there are no studies of safety and risks with estrogen concentrations attained in combination treatment.

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 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 with the appropriate medication before the start of treatment with <invented name>.

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 <invented name>, in particular:
– Leiomyoma (uterine fibroids) or endometriosis;
– Risk factors for thromboembolic disorders (see below);
– Risk factors for estrogen dependent tumours, e.g. 1st degree heredity for breast cancer;
– Hypertension;

- Liver disorders (e.g. liver adenoma);
- Diabetes mellitus with or without vascular involvement;
- Cholelithiasis;
- Migraine or (severe) headache;
- Systemic lupus erythematosus (SLE);
- 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 headaches;
- Pregnancy.

Endometrial hyperplasia and carcinoma
An increased risk of endometrial hyperplasia or uterine cancer has not been attributed to treatment with estriol by vaginal use.
In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when systemic estrogens are administered alone for prolonged periods.

For estrogen products for vaginal application of which the systemic exposure to estrogen is very low, it is not recommended to add a progestagen.

Endometrial safety of long-term (more than one year) or repeated use of local vaginally administered estrogen is uncertain. Therefore, if repeated, treatment should be reviewed at least annually.

Unopposed estrogen 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 following risks have been associated with **systemic** HRT and apply to a lesser extent for estrogen products for vaginal application of which the systemic exposure to the estrogen is very low. 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 estrogens. It is unknown if low dose vaginal estrogens stimulate recurrence of breast cancer.

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 estrogen-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 estrogens, 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' (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 (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD)

Estrogen-only

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

Ischaemic stroke

Systemic estrogen-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

Estrogens may cause fluid retention and therefore patients with cardiac or renal dysfunction should be carefully observed.

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 estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

Estrogens 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 biologically 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.

Note
<Invented name> cannot be used for contraception.

The excipient butylhydroxytoluene may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

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 <invented name>. However interactions with other locally applied vaginal treatments should be considered.

If <invented name> is used simultaneously with condoms made of latex it can decrease the tensile strength and thus impair the safety of condoms.

4.6 Fertility, pregnancy and lactation

Pregnancy
<Invented name> is not indicated during pregnancy. If pregnancy occurs during medication with <invented name> treatment should be withdrawn immediately.
The results of most epidemiological studies to date relevant to inadvertent fetal exposure to estrogens indicate no teratogenic or fetotoxic effects. However, no clinical data on fetal exposure following vaginal administration of estriol are available. Given the high estriol concentrations in human pregnancy, any fetal exposure to estriol due to the use of low-dose pessaries is to be regarded as negligible.

Breastfeeding
<Invented name> is not indicated during lactation. However, very low doses of vaginally applied estriol are unlikely to interfere with lactation.

4.7 Effects on ability to drive and use machines

<Invented name> has no influence on the ability to drive and use machines.

4.8 Undesirable effects

At the beginning of treatment, when the vaginal epithelial layers are still atrophic, local irritation may occur as a sensation of heat, pain and/or itching but the undesirable effects are often transient and of mild intensity.

The reported undesirable effects have been classified according to frequency of appearance:

System Organ Class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)
Gastrointestinal disorders		anorectal discomfort

Renal and urinary disorders	dysuria	
Reproductive system and breast disorders	vulvovaginal burning, pruritus and pain	vaginal discharge

Class effects associated with systemic HRT
The following risks have been associated with systemic HRT and apply to a lesser extent for estrogen products for vaginal application of which the systemic exposure to estrogen is very low.

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 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 & 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 & 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 **systemic** oestrogen/progestagen treatment:
- 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 [To be completed nationally].

4.9 Overdose

Toxicity for estriol is very low. Overdose of <invented name> by vaginal application is very unlikely. Symptoms that may occur in the case of a high dose is accidentally ingested are nausea, vomiting and vaginal bleeding in females. There is no known antidote. If necessary, a symptomatic treatment should be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: natural and semisynthetic estrogens, plain, ATC code: G03CA04

The active ingredient, semisynthetic estriol, is chemically identical to human estriol which is produced naturally in the body. Vaginally applied estriol alleviates the symptoms of vaginal atrophy due to estrogen deficiency in postmenopausal women. Instead of an atrophic cell profile mainly intermediate cells and an increasing number of superficial cells are found in the vagina; inflammatory disorders disappear and restoration of the vaginal Lactobacillus flora (Doederlein's flora) is supported. Superiority of <invented name> over placebo in the local treatment of vaginal atrophy was shown in a randomized double-blind clinical trial involving 438 postmenopausal women. Intravaginal administration of low-dose <invented name> resulted in a significant improvement of objective efficacy variables (vaginal maturation index, vaginal pH) as well as in a considerable alleviation of subjective symptoms (Most Bothersome Symptoms / MBS) after 12 weeks of treatment (p-value < 0.001 for all 3 parameters).

5.2 Pharmacokinetic properties

Absorption and distribution
A pharmacokinetic study was performed in postmenopausal women with diagnosed vaginal atrophy in order to investigate the extent of systemic exposure to estriol from <invented name>. Treatment was by the vaginal route once daily for 21 days. A single dose of 0.03 mg estriol increased mean estriol peak plasma concentration (C_{max}) to 42.11 pg/ml one hour after dosing. Twelve hours after administration the estriol concentration had decreased to below 5 pg/ml (LLoQ) in all patients. After daily treatment for 21 days the peak concentration was 11.9 pg/ml two hours after dosing. This value remains in the range of postmenopausal estriol plasma concentrations. The average concentration (C_{av}) after multiple dosing was 2.2 pg/ml.
In plasma about 8 % of estriol is available in its free form, 91 % is bound to albumin and 1 % to SHBG.

Biotransformation
Metabolism in the liver mainly leads to glucuronides and sulfates.

Elimination
Estriol is mainly excreted in its conjugated form via the kidneys and in a small fraction via the bile.

5.3 Preclinical safety data

The toxicological properties with estrogens are well known. Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic

potential, beyond that which has already been considered in other sections of this summary of product characteristics.

Preclinical data are not available for vaginal administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylhydroxytoluene
Glycerolmono/bis[(Z-R)-12-hydroxyoctadec-9-enoate]
Hard fat
Macrogol cetostearyl ether

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

Aluminium/laminated PE strips with pessaries packed in a cardboard carton.
Pack sizes with 10, 15, 20, 24 and 30 pessaries.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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12277 Berlijn
Duitsland

8. MARKETING AUTHORISATION NUMBER

RVG 121712

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