1. NAME OF THE MEDICINAL PRODUCT
Gynokadin® Dosage Gel
0.6 mg/g Gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 g Gel contains 0.62 mg estradiol hemihy-drate (equivalent to 0.6 mg estradiol).
Excipients with known effect
This medicinal product contains 0.5 g alcohol (ethanol) per dose of 1.25 g Gel.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Gel
Translucent, slightly opalescent gel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
- For the treatment of symptoms due to declining estradiol production by the ovaries during and after menopause or after oophorectomy (climacteric syndrome),
- for the treatment of estrogen deficiency-related regression symptoms in the urinary and genital organs.

The use of this medicinal product alone (without regular addition of progestogens) for treatment during and after menopause should only be in women who have undergone a hysterectomy.

4.2 Dosage and method of administration
Dosage
For both the initiation and continuation of treatment for estrogen deficiency symptoms, the lowest effective dose for the shortest possible duration of therapy should be used (see section 4.4).

Typically, 2.5 g of Gynokadin Dosage Gel (equivalent to 2 dosing units) is applied once daily.

Patients previously treated with oral estrogens should start using Gynokadin Dosage Gel one week after discontinuing the tablets or as soon as symptoms reappear; the dosage should be adjusted individually during the course of therapy.

Breast tenderness is considered a sign of an excessively high dose; treatment should then be continued with a reduced dose. If symptoms do not improve after a few weeks, the dose can be increased (up to 5 g of Gynokadin Dosage Gel, equivalent to 4 dosing units). The dosage should be regularly reviewed depending on the extent of hormonal deficiency symptoms.

Gynokadin Dosage Gel should generally be used cyclically, with 3 weeks of daily gel application followed by a treatment-free week. If menstrual bleeding is still present, treatment should start in

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alignment with the cycle, beginning on the 5th day after the start of menstruation. If there is no more menstrual bleeding, therapy can be started at any time.

Continuous non-cyclical use of Gynokadin Dosage Gel can occur in cases where estrogen deficiency symptoms are too severe during the treatment-free week. Continuous therapy is also indicated for women after surgical removal of the ovaries.

Long-term use of Gynokadin Dosage Gel during menopause should be supplemented with the regular administration of a progestogen according to medical instructions in women with an intact uterus. The progestogen should be taken from the 10th day of Gynokadin Dosage Gel application and continued for 12 days until the start of the treatment-free week (cyclical substitution). In women with an intact endometrium, regular withdrawal bleeding may occur during the therapy-free week after discontinuing Gynokadin Dosage Gel and the progestogen preparation. In hysterectomized women, the addition of a progestogen is not recommended, except in cases where endometriosis has been diagnosed (see section 4.4).

Method of administration
For correct dosing of Gynokadin Dosage Gel with the dosing dispenser, the following procedure is recommended: When pressing down the dosing head, the gel strand is fully dispensed (equivalent to 1 dosing unit). Each dosing unit contains 1.25 g of gel. The button should be pressed multiple times according to the desired dosage, and then the gel should be applied and rubbed into the appropriate skin areas with the fingers.

When starting the dosing dispenser, it is possible that the first dose does not exactly correspond to one dosing unit, so it is recommended to discard the first dose.

After dispensing, the dosing dispenser should always be closed.

The dosing dispenser can dispense 64 individual doses (equivalent to 32 days when using the normal dose of 2.5 g gel (2 dosing units) daily). Gynokadin Dosage Gel should be applied to as large an area as possible, preferably on arms and shoulders. The normal dose of 2.5 g gel (2 dosing units) should be applied to the entire arm including the shoulder (approximately 1500 cm2) and gently rubbed in. For 5 g gel (4 dosing units), both arms should be used.

If the dose is to be reduced, 1 dosing unit can be used; for dose increase, up to 4 dosing units can be applied.

After application, hands must be thoroughly washed with water and soap.

Gynokadin Dosage Gel should not be applied to the genital area, breasts, or mucous membranes.

The gel dries completely and invisibly on the skin within 2 – 3 minutes, and clothing should not be put on until after drying.

Patients should be informed that children should not come into contact with the body area where the estradiol gel was applied (see section 4.4).

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4.3 Contraindications
– Existing or previous breast cancer or a corresponding suspicion;
– Estrogen-dependent malignant tumor or a corresponding suspicion (e.g., endometrial carcinoma);
– Unexplained genital bleeding;
– Untreated endometrial hyperplasia;
– Previous or existing venous thromboembolic disorders (deep vein thrombosis, pulmonary embolism);
– Known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency, see section 4.4);
– Existing or recent arterial thromboembolic disorders (e.g., angina pectoris, myocardial infarction);
– Acute liver disease or past liver disease as long as the relevant liver enzyme levels have not normalized;
– Porphyria;
– Hypersensitivity to the active substance or any of the other ingredients listed in section 6.1.

4.4 Special warnings and precautions for use
Hormone replacement therapy (HRT) should only be initiated for the treatment of postmenopausal symptoms that adversely affect quality of life. Benefits and risks should be carefully weighed against each other at least annually in each individual case, and HRT should only be continued as long as the benefits outweigh the risks.

There is limited data to assess the risks of HRT in premature menopause; however, since the absolute risk is lower in younger women, the benefit-risk ratio may be more favorable in younger women than in older women.

Medical examination/control examinations
Before starting or resuming HRT, a complete personal and family medical history of the patient should be obtained. The physical examination (including abdomen and breast) should be guided by these histories as well as the contraindications and warnings. Regular control examinations are recommended during treatment, which should be tailored in frequency and type to the individual risk situation of the woman. Women should be informed about which breast changes they need to report to the doctor (see 'Breast cancer' below). Examinations, including appropriate imaging techniques such as mammography, should be conducted according to current preventive practices and the clinical needs of the individual woman.

Situations requiring monitoring
Patients should be closely monitored if any of the following situations or conditions are present or have occurred in the past, or worsened during a pregnancy or previous hormone treatment. It should be considered that these situations or conditions may recur or worsen during hormone replacement therapy with Gynokadin Dosiergel:
– Leiomyoma (uterine fibroids) or endometriosis;
– Risk factors for thromboembolism (see below);
– Risk factors for estrogen-dependent tumors, e.g., occurrence of breast cancer in first-degree relatives;
– Hypertension;

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– Liver diseases (e.g., liver adenoma);
– Diabetes mellitus with or without vascular involvement;
– Cholelithiasis;
– Migraine or (severe) headaches;
– Systemic lupus erythematosus (SLE); – History of endometrial hyperplasia (see below);
– Epilepsy;
– Asthma;
– Otosclerosis.

Reasons for immediate discontinuation of therapy
Therapy should be discontinued upon the occurrence of a contraindication and in the following situations:
– Jaundice or deterioration of liver function;
– Significant increase in blood pressure;
– Onset of migraine-like headaches;
– Pregnancy.

Endometrial hyperplasia and cancer
In women with an intact uterus, the risk of endometrial hyperplasia and carcinoma is increased with long-term estrogen monotherapy. The reported increase in the risk of developing endometrial carcinoma in users of estrogen monotherapy ranges from a 2-fold to a 12-fold increase compared to women without HRT, depending on the duration of use and the dose of estrogen (see section 4.8). After discontinuation of treatment, the risk may remain elevated for at least 10 years. The additional cyclic administration of a progestogen for at least 12 days per month or per 28-day cycle, or continuous combined estrogen-progestogen treatment in women with an intact uterus, compensates for the additional risk posed by estrogen monotherapy.

Breakthrough and spotting bleeding may occur during the first months of treatment. If such bleeding occurs later in the course of therapy or persists after therapy ends, the cause must be investigated and, if necessary, an endometrial biopsy should be performed to exclude malignant endometrial disease.

Endometriosis
Unopposed estrogen stimulation can lead to a premalignant or malignant transformation of residual endometriosis foci, therefore, it should be considered to give a progestogen in addition to estrogen replacement therapy in cases where a hysterectomy has been performed due to endometriosis and residual endometriosis is present.

Breast cancer
There is evidence of an increased risk of breast cancer in women receiving combined HRT with estrogen and progestogen or HRT with estrogen alone, this risk depends on the duration of HRT.

Combined therapy with estrogen and progestogen:
In the randomized, placebo-controlled Women's Health Initiative Study (WHI) and a meta-analysis of prospective epidemiological studies, an increased risk of breast cancer was equally found in women taking a combination of estrogen and progestogen as HRT, this risk appears after about 3 (1 – 4) years (see section 4.8).

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HRT with estrogen only:
The WHI study showed no increased risk of breast cancer in hysterectomized women under estrogen monotherapy, observational studies have mostly shown a slightly increased risk of a breast cancer diagnosis, which was, however, lower than the risk in users of estrogen-progestogen combinations (see section 4.8).

The results of a large meta-analysis have shown that after the end of treatment, the increased risk decreases over time and the time to return to the age-appropriate baseline risk depends on the duration of previous HRT use, if HRT was used for more than 5 years, the risk may persist for a period of 10 years or longer.

HRT, especially combined treatment with estrogens and progestogens, leads to increased breast density in mammography, which can adversely affect radiological breast cancer diagnostics.

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 estrogen-only or combined estrogen-progestogen medications as part of HRT, which appears within 5 years of use and decreases over time after treatment ends, some other studies, including the WHI study, suggest that the corresponding risk with combined HRT is comparable or slightly lower (see section 4.8).

Venous thromboembolism
HRT is associated with a 1.3 to 3-fold increased risk of venous thromboembolism (VTE), i.e., deep vein thrombosis or pulmonary embolism, in the first year of HRT, the occurrence of a VTE is more likely than later (see section 4.8).

Patients with known thrombophilia have an increased VTE risk, HRT can increase this risk and is therefore contraindicated in these patients (see section 4.3).

Generally recognized VTE risk factors include the use of estrogens, older age, major surgery, prolonged immobilization, significant overweight (BMI > 30 kg/m2), pregnancy/postpartum, systemic lupus erythematosus (SLE), and cancer, there is no consensus on the possible role of varicose veins in VTE, as with all postoperative patients, preventive measures to prevent a VTE after surgery must be considered, in the case of prolonged immobilization after planned surgery, it is recommended to discontinue HRT 4 to 6 weeks before the procedure, treatment should only be resumed when the woman is fully mobilized again.

In women without a history of VTE but with first-degree relatives who developed VTE at a young age, thrombophilia screening may be considered, the patient should be thoroughly informed about the limited significance of this procedure beforehand (only a portion of the defects leading to thrombophilia are identified), if a thrombophilic defect is found and thromboses are also known in relatives or the identified defect is severe (e.g., antithrombin, protein S, and/or protein C deficiency or a combination of defects), HRT is contraindicated (see section 4.3).

In patients on long-term anticoagulant therapy, the benefit-risk ratio should be carefully weighed before using HRT.

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If a VTE develops after starting HRT, the medication must be discontinued, patients should be advised to contact a doctor immediately if they notice possible symptoms of thromboembolism (especially painful swelling of a leg, sudden chest pain, shortness of breath).

Coronary heart disease
There is no evidence from randomized controlled trials that combined HRT with estrogen and progestogen or estrogen monotherapy protects women from a myocardial infarction, regardless of whether they have coronary heart disease or not.

Combined therapy with estrogen and progestogen:
The relative risk of coronary heart disease is slightly increased under combined HRT with estrogen and progestogen, as the baseline risk for coronary heart disease is highly age-dependent, the number of additional cases attributable to HRT with estrogen and progestogen is very low in premenopausal healthy women, but the number increases with age.

HRT with estrogen only:
Randomized controlled trials found no evidence of an increased risk of coronary heart disease in hysterectomized women under estrogen monotherapy.

Ischemic stroke
Combined treatment with estrogen and progestogen and estrogen monotherapy are associated with up to a 1.5-fold increased risk of ischemic stroke, the relative risk is independent of age and the time since menopause, however, as the baseline risk of stroke is highly age-dependent, the overall risk of stroke for women under HRT increases with age (see section 4.8).

Other conditions
Estrogens can cause fluid retention, therefore patients with cardiac or renal dysfunction should be carefully monitored.

Women with pre-existing hypertriglyceridemia must be closely monitored during estrogen or hormone replacement therapy, as rare cases of marked plasma triglyceride elevation leading to pancreatitis have been reported in association with estrogen therapy under such circumstances.

Exogenously administered estrogens can trigger or worsen symptoms of hereditary and acquired angioedema.

Estrogens increase the concentration of thyroxine-binding globulin (TBG), leading to an increase in total circulating thyroid hormone, which is measured by protein-bound iodine (PBI), T4 levels (column or radioimmunoassay), or T3 levels (radioimmunoassay), T3 resin uptake is decreased, reflecting an increase in TBG, free T4 and T3 concentrations remain unchanged, other binding proteins may be increased in serum, such as corticosteroid-binding globulin (CBG) and sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids or sex hormones, free or biologically active hormone concentrations remain unchanged, other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

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Cognitive abilities do not improve under HRT, there is evidence of an increased risk of probable dementia in women who were older than 65 years at the start of continuous combined HRT or estrogen monotherapy.

ALT elevations
In clinical studies with patients whose hepatitis C virus infections (HCV) were treated with the combination regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, an increase in ALT more than 5 times the upper limit of normal (ULN) occurred significantly more often in women using ethinylestradiol-containing medications such as CHC, ALT elevations were also observed in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir in women using ethinylestradiol-containing medications like CHC, in women using medications with estrogens other than ethinylestradiol, such as estradiol, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, the rate of elevated ALT values was similar to those not receiving any estrogens, due to the limited number of women using these other estrogens, caution is still advised when co-administering with the following combination regimens: ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin and with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.5).

Possible transmission of estradiol to children
Estradiol gel can be accidentally transferred from the application site to children, post-marketing reports have noted breast development and breast masses in prepubertal girls, early puberty, gynecomastia, and breast masses in prepubertal boys after accidental secondary exposure to estradiol, in most cases, these symptoms regressed after discontinuing estradiol exposure.

Patients should be instructed: – not to allow others, especially children, to come into contact with the exposed skin area and to cover the application site with clothing if necessary, in case of contact, the child's skin should be washed immediately with water and soap, – to consult a doctor if signs and symptoms (breast development or other sexual changes) occur in a child who may have been accidentally exposed to estradiol gel.

Other information
Gynokadin Dosage Gel has no contraceptive effect, if the use of estradiol is unavoidable, non-hormonal contraception should be used.

This medicine contains 0.5 g of alcohol (ethanol) per dose of 1.25 g gel, on damaged skin it may cause a burning sensation, the medicine is flammable until completely dried.

4.5 Interactions with other medicinal products and other forms of interaction
The metabolism of estrogens can be increased by the simultaneous use of substances that induce drug-metabolizing enzymes, especially cytochrome P450 enzymes, these substances include anticonvulsants (e.g., phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g., rifampicin, rifabutin, nevirapine, efavirenz), ritonavir and nelfinavir have enzyme-inducing properties when used concurrently with steroid hormones, although they are known as strong enzyme inhibitors, herbal medicines containing St. John's wort (Hypericum perforatum) can induce the metabolism of estrogens.

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Clinically, increased estrogen metabolism can lead to a reduced effect of estrogen and changes in the uterine bleeding pattern.

With transdermal application, the first-pass effect in the liver is bypassed, so transdermally applied estrogens may be less affected by enzyme inducers than orally administered hormones.

The simultaneous intake of ascorbic acid and estrogens can enhance the effect of estrogens, while the use of phenylbutazones simultaneously with oral estrogens can reduce their effect.

Effect of HRT with estrogens on other medicinal products
It has been shown that estrogen-containing hormonal contraceptives significantly reduce plasma concentrations of lamotrigine due to the induction of lamotrigine glucuronidation when administered concurrently, this can impair seizure control, although the possible interaction between hormone replacement therapy and lamotrigine has not been studied, it is assumed that a similar interaction exists, which may lead to a reduction in seizure control in women using both medications together.

Concurrent use of oral estrogens with metoprolol or imipramine may enhance or prolong the effects of these agents.

Concurrent use of oral estrogens and paracetamol, benzodiazepines such as lorazepam and temazepam, anticoagulant and hypoglycemic substances may weaken the effects of these medications.

Laboratory tests
Glucose tolerance, blood coagulation, metyrapone, and thyroid function tests may be affected.

Pharmacodynamic interactions
Direct-acting antiviral drugs (DAAs) and ethinylestradiol-containing drugs such as COCs
In clinical studies with the combination regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin against HCV, an increase in ALT more than 5 times the upper limit of normal (ULN) occurred significantly more frequently in women using ethinylestradiol-containing drugs such as COCs, furthermore, ALT elevations were also observed in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir in women taking ethinylestradiol-containing drugs such as COCs.
Direct-acting antiviral drugs (DAAs) and drugs containing estrogens other than ethinylestradiol, such as estradiol
In women using drugs with estrogens other than ethinylestradiol, such as estradiol, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, the rate of elevated ALT levels was similar to those not receiving any estrogens, due to the limited number of women using these other estrogens, caution is still advised when co-administering with the following combination regimens: ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin and with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.4).

4.6 Fertility, pregnancy and lactation
Pregnancy

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Gynokadin dosage gel is not indicated during pregnancy. If pregnancy occurs during treatment with Gynokadin dosage gel, the treatment should be discontinued immediately. Most of the current epidemiological studies relevant to unintended estrogen exposure of the fetus show no teratogenic or fetotoxic effects.

Lactation
Gynokadin dosage gel is not indicated during lactation.

4.7 Effects on the ability to drive and use machines
Gynokadin dosage gel has no influence on the ability to drive and use machines.

4.8 Side effects
Side effects that may occur during treatment with Gynokadin dosage gel are listed in Table 1, organized by organ classes.

Note:
In treatment with Gynokadin dosage gel without progestogens, breakthrough bleeding may occur in case of overdose. In combined use of Gynokadin dosage gel and a progestogen, withdrawal bleeding usually occurs after the progestogen treatment period.

Breast cancer risk
In women who had undergone combined estrogen-progestogen therapy for more than 5 years, the risk of a breast cancer diagnosis was up to 2 times higher. In users of estrogen monotherapy, the increase in risk is lower than in users of estrogen-progestogen combination preparations. The level of risk depends on the duration of use (see section 4.4).

Estimates of absolute risk based on the results of the largest randomized, placebo-controlled study (WHI study) and the largest meta-analysis of prospective epidemiological studies to date are presented: See Tables 2, 3, and 4.

Endometrial cancer risk
Postmenopausal women with an intact uterus
Approximately 5 out of 1,000 women with an intact uterus who do not use HRT develop endometrial cancer. In women with an intact uterus, the use of estrogen monotherapy is not recommended as it increases the risk of endometrial cancer (see section 4.4). Depending on the duration of estrogen monotherapy and the estrogen dose, the increased risk of endometrial cancer in epidemiological studies was between 5 and 55 additional diagnosed cases per 1,000 women aged 50 to 65 years. By adding a progestogen to the estrogen monotherapy for at least 12 days per cycle, this increased risk can be avoided. In the Million Women Study, after 5 years of using combined HRT (sequential or continuous), the risk of endometrial cancer was not increased (RR 1.0 (95% CI 0.8 – 1.2)).

By adding a progestogen to estrogen monotherapy for at least 12 days per cycle, this increased risk can be avoided; in the Million Women Study, after 5 years of using combined HRT (sequential or continuous), the risk of endometrial carcinoma was not increased (RR 1.0 (95% CI 0.8 – 1.2)).

Ovarian cancer risk

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The use of estrogen-only or combined estrogen-progestogen medicines for HRT is associated with a slightly increased risk of being diagnosed with ovarian cancer (see section 4.4), a meta-analysis of 52 epidemiological studies indicates an increased risk of ovarian cancer for women currently using HRT compared to women who have never used HRT (RR 1.43; 95% CI 1.31 – 1.56), in women aged 50 to 54 years who use HRT for 5 years, approximately one additional case per 2,000 users occurs, in women aged 50 to 54 years who do not use HRT, about 2 cases of ovarian cancer per 2,000 women are diagnosed over a 5-year period.

Risk of venous thromboembolism
The risk of developing a venous thromboembolism (VTE), i.e., a thrombosis of the deep leg or pelvic veins or a pulmonary embolism, is increased 1.3 to 3 times with HRT. The occurrence of such an event is more likely during the first year of treatment than in subsequent years (see section 4.4). The relevant results of the WHI studies are shown in Table 5.

Risk of coronary heart disease
In users of combined estrogen-progestogen HRT over the age of 60, the risk of developing coronary heart disease is slightly increased (see section 4.4).

Risk of ischemic stroke
The use of estrogen monotherapy or combined estrogen-progestogen therapy is associated with up to a 1.5-fold increased risk of ischemic stroke. The risk of hemorrhagic stroke is not increased with HRT. This relative risk is independent of age or duration of use. However, since the baseline risk strongly depends on age, the overall risk increases with age in women on HRT (see section 4.4).

See Table 6.

Other adverse drug reactions have been observed in connection with estrogen-progestogen treatment: – Skin and subcutaneous disorders: erythema multiforme, erythema nodosum, vascular purpura; – probable dementia in women over 65 years of age (see section 4.4).

Reporting of suspected adverse reactions
The reporting of suspected adverse reactions after approval is of great importance. It enables continuous monitoring of the benefit-risk ratio of the medicinal product. Healthcare professionals are encouraged to report any suspected adverse reactions to the Federal Institute for Drugs and Medical Devices, Dept. Pharmacovigilance, Kurt-Georg-Kiesinger-Allee 3, D-53175 Bonn, Website: www.bfarm.de.

4.9 Overdose
a) Symptoms of overdose
Breast tension and pain, cervical discharge, genital bleeding, nausea, and vomiting may be signs of relative overdose. They can also occur in children and young girls after taking higher doses of estrogen. Due to the very low toxicity of estradiol, further toxic effects are not expected.

b) Therapeutic measures in case of overdose
The mentioned symptoms are only temporary, do not require specific treatment, and can be eliminated by dose reduction or discontinuation of therapy. A specific antidote is not known.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Estrogens, ATC code: G03CA03

The active ingredient, synthetic 17β-estradiol, is chemically and biologically identical to endogenous human estradiol, substitutes for the loss of estrogen production in menopausal women, and alleviates the associated symptoms.

5.2 Pharmacokinetic properties

Absorption

After dermal application of Gynokadin Dosage Gel, estradiol enters the bloodstream directly through transdermal diffusion, avoiding the first liver passage and thus preventing the massive metabolism to estrone known from oral administration.

With continuous medication, a bioavailability between 5% and 6% can be assumed.

Distribution

With once-daily application of Gynokadin Dosage Gel, the serum level of estradiol reaches equilibrium after a few days, the height of which is dose-dependent. When applying 1.5 mg estradiol (equivalent to 2.5 g gel), the mean estradiol level was in the range of 60 – 80 pg/ml, for estrone, an average of about 50 pg/ml was measured in the steady state, corresponding to an estrone:estradiol ratio of about 1, which is within the physiological range for fertile women before menopause. When applying 5 g Gynokadin Dosage Gel (3 mg estradiol) on the same application area as with 2.5 g gel, approximately 70% higher blood levels are achieved. The absolute estrone and estradiol levels during treatment with 2.5 g Gynokadin Dosage Gel are within the range of the mid to late follicular phase of an ovulatory cycle.

With low-dose application of Gynokadin Dosage Gel (0.75 mg estradiol, equivalent to 1.25 g gel), median estradiol concentrations of 32 and 33.5 pg/ml were observed after 12 weeks of application in two multicenter, randomized, double-blind studies. In another pharmacokinetic study with 24 postmenopausal women using 0.75 mg estradiol, equivalent to 1.25 g gel (1 dose pump of Gynokadin Dosage Gel), once daily over a total of 14 days, a mean serum concentration (cavg) of estradiol of 28.3 pg/ml was determined over time, and a daily available systemic amount of 35.1 µg estradiol was calculated.

Biotransformation and elimination

Estradiol is primarily metabolized in the liver, where estrone and estriol, both free or bound as glucuronides or sulfates, are formed. They are less effective than estradiol. The excretion of glucuronides and sulfates occurs mainly via urine.

5.3 Preclinical safety data

Due to the pronounced differences between animal species and in relation to humans, animal experimental results with estrogens have only limited predictive value for human application.

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In experimental animals, estradiol or estradiol valerate showed an embryolethal effect even at relatively low doses. Malformations of the urogenital tract and feminization of male fetuses were observed.

Toxicity studies with Gynokadin Dosage Gel were conducted on mice, rats, guinea pigs, and rabbits. In rabbits, doses equivalent to 16 – 32 µg/kg estradiol were applied dermally over 4 weeks and 100 µg/kg over 5 days, in mice a single dose of 800 – 1000 µg/kg, in rats 25 – 75 µg/kg over 3 – 4 weeks, and in guinea pigs 1.5 – 4 mg/kg multiple times. No local intolerances occurred in these experiments, and a significant increase in uterine weight with typical morphological changes of estrogen stimulation was observed.

Based on conventional studies on repeated dose toxicity, genotoxicity, and carcinogenic potential, the preclinical data do not reveal any special hazards for humans beyond those already described in other sections of this product information.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer 980 NF, ethanol 96%, trolamine, purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years, shelf life after opening: 3 months.

6.4 Special precautions for storage

No special storage conditions are required for this medicinal product.

6.5 Nature and contents of container

Dispenser, OP with 80 g gel N 1, OP with 240 g gel (3 × 80 g) N 3.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORIZATION HOLDER

Besins Healthcare Germany GmbH, Mariendorfer Damm 3, 12099 Berlin, Phone: +49 30 408199-0, Fax: +49 30 408199-100, Email: medizin@besins-healthcare.com, www.besins-healthcare.de.

8. MARKETING AUTHORIZATION NUMBER

52958.00.00

9. DATE OF AUTHORIZATION/RENEWAL OF AUTHORIZATION

Date of authorization: 30 June 2005, Date of last renewal of authorization: 20 August 2012.

10. DATE OF REVISION OF THE TEXT

September 2025.

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11. SALES RESTRICTION

Prescription only.

Rote Liste Service GmbH, September 2025, www.fachinfo.de, Mainzer Landstraße 55, 60329 Frankfurt.

Table 1

System organ class	Occasionally (≥ 1/1,000, < 1/100)	Rarely (≥ 1/10,000, < 1/1,000)	Very rarely (< 1/10,000)
Nervous system disorders		migraine-like headaches	
Eye disorders			Contact lens intolerance (possibly requiring re-fitting of contact lenses)
Vascular disorders			Worsening or inflam-development of varicose veins; increase in blood pressure
diseases of the gastrointestinal tract		gastrointestinal complaints (e.g. nausea, bloating)	
liver and gallbladder diseases		diseases of the gallbladder	cholestasis; increased risk of cholelithiasis; liver dysfunction
diseases of the skin and subcutaneous tissue	local skin irritations (itching, skin redness, rash); chloasma		
diseases of the reproductive organs and the breast	breast tenderness; vaginal discharge	mastopathy	
General disorders and complaints at the administration site	extracellular water retention, edema formation		
Investigations	Weight gain		

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Table 2
Largest meta-analysis to date of prospective epidemiological studies
Estimated additional breast cancer risk after 5 years of use in women with a BMI of 27 (kg/m2)

Age at the start of HRT (years)	Incidence per 1,000 non-users of HRT over a period of 5 years (50 – 54 years)*	Relative risk	Additional cases per 1,000 HRT-Users after 5 years
HRT with estrogen only			
50	13.3	1.2	2.7
Combined therapy with estrogen and progestogen			
50	13.3	1.6	8.0

* based on the baseline incidence rates in England in 2015 for women with a BMI of 27 (kg/m2)
Note: As the background incidence of breast cancer varies by EU country, the number of additional breast cancer cases also changes proportionally.

Table 3
Estimated additional breast cancer risk after 10 years of use in women with a BMI of 27 (kg/m2)

Age at the start of HRT (years)	Incidence per 1,000 Non-users of an HRT over a period of 5 years (50 – 59 years)**	Relative risk	Additional cases per 1,000 HRT users after 10 years
HRT with estrogen only			
50	26.6	1.3	7.1
Combined therapy with estrogen and progestogen			
50	26.6	1.8	20.8

** based on the baseline incidence rates in England in 2015 for women with a BMI of 27 (kg/m2)
Note: Since the background incidence of breast cancer varies by EU country, the number of additional breast cancer cases also changes proportionally. Table 4

Table 4
Age group

(years) Incidence	per 1,000 women in the placebo arm over a period of 5 years	(95% CI) Additional cases	per 1,000 HRT users over a period over a period

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	Relative risk		of 5 years (95% CI)
Estrogen monotherapy (CEE)			
50 – 79	21	0.8 (0.7-1.0)	-4 (-6-0) +
Estrogen + Progestin (CEE + MPA)‡			
50 – 79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)

+ WHI study in women without a uterus, which did not show an increased risk of breast cancer.
‡ When limiting the analysis to women who had not used HRT before the study, the risk did not appear increased during the first 5 years of treatment: After 5 years, the risk was higher than in untreated women.

Table 5
WHI studies – additional risk of VTE after 5 years of use

Age group (years)	Incidence per 1,000 women in the placebo arm over a period of 5 years	Relative risk (95% CI)	Additional cases per 1,000 HRT users over a period of 5 years
Oral estrogen monotherapy***			
50 – 59	7	1.2 (0.6 – 2.4)	1 (-3 – 10)
Combined oral estrogen-progestogen therapy			
50 – 59	4	2.3 (1.2 – 4.3)	5 (1 – 13)

*** Study in Women Without Uterus

Table 6
Combined WHI Studies – Additional Risk of Ischemic Stroke**** after

5-year Use	Incidence per 1,000 Women in the Placebo Arm over 5 Years	Relative Risk (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 distinction was made between ischemic and hemorrhagic stroke.

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