INSTRUCTION
on medical use of
OESTROGEL

Composition:

active ingredient: estradiol;
1 g of gel contains 0.6 mg of estradiol (as estradiol hemihydrate);
excipients: carbomer 980, triethanolamine, 96% ethanol, purified water.

Each dose of the applicator corresponds to 2.5 g of gel or 1.5 mg of estradiol.

Pharmaceutical form.
Gel for local application.

Pharmaceutical group.
Estrogens. Simple preparations of natural and semisynthetic estrogens.
ATC code G03 C03.

Clinical characteristics.
Indications.
The symptoms related to deficiency of estrogens during age-related or artificial menopause, for prevention of osteoporosis.

Contraindications.
History of increased sensitivity to the active ingredient or excipients.
Breast cancer (diagnosed, suspected or history thereof).
Diagnosed or suspected estrogen-dependent malignant tumors (e.g., endometrium cancer).
Vaginal bleedings of non-established etiology.
Untreated endometrial hyperplasia.
Current or history of thromboembolic diseases of the veins (deep vein thrombosis (DVT), pulmonary artery embolism).
Current or history of acute thromboembolism of the arteries (e.g., angina pectoris, myocardial infarction).
Current or history of severe liver impairment (before normalization of laboratory parameters of the liver function).
Porphyria.

Administration and dosage.
Oestrogel is administered by cycles of 24-28 days per month. Doses and duration of treatment are determined by the doctor individually. One dose (2.5 g of gel) is applied in a thin layer on a large area of the skin: of the abdomen, low back, hips, shoulders and arms until complete absorption once daily. Usually 2.5 g of gel per day are used. If necessary, after 2-3 cycles the dose may be adjusted in accordance with the clinical signs of excess or deficiency estrogens (see section "Side reactions"). At the end of each therapeutical cycle menstruation-like bleedings of withdrawal are possible to occur.

**Administration**

1 dose of the applicator corresponds to 2.5 g of gel or 1.5 mg of estradiol hemihydrate.

The gel is applied by the patient herself. For use open the tube and punch it with a small puncheon located in the stopper. The metal membrane of the tube must be fully opened. Use a plastic applicator-dispenser for measuring a daily dose. Press the tube above the spatula ruler. 1 dose is equal to a column (the diameter of a pencil), the length of which coincides with an indent on the ruler. The indent has a score which allows to divide the daily dose in 2 parts. One tube contains 30 doses. The gel should be applied with a thin layer in the above specified areas. Do not massage the site of the gel application. The gel contact with the breasts and mucosae should be avoided. Application is considered to be correct if the gel is absorbed completely within 2-3 minutes.

**Side reactions.**

As a rule, side reactions are poorly pronounced and require discontinuation of treatment very rarely. Side reactions usually occur only in the first months of treatment.

*Disorders of metabolism:* edemas, an increase of body mass.
*Psychic disturbances:* changes in mood and disorders of libido.
*Nervous system:* headache, migraine.
*Cardiovascular system:* an increase of blood pressure, venous thromboembolism.
*Digestive tract:* nausea, vomiting, gastric colic, liver dysfunction and disorders of bile outflow.
*Skin:* eruptions.
*Reproductive system:* irregular vaginal bleedings or discharges.
*Neoplasms in the breasts:* breast cancer.
*Reactions at the site of application:* skin irritation.
Below side effects are given which require the dose adjustment depending on signs of deficiency or increased amount of estrogens:

*signs of estrogen deficiency:* flushes, frequent headache, migraine, dryness of the vagina, irritation of the eyes during the use of contact lenses;

*signs of excessive amount of estrogens:* nausea, vomiting, abdominal gripes, flatulence, swelling of the breasts, irritability, edemas, heaviness of the legs, increased secretions from the uterine cervix.

*Other possible side effects:* uterine bleedings (it is necessary to determine the cause, including endometriosis), galactorrhea (examination is necessary to exclude adenoma of the pituitary body), exacerbation of epilepsy, chloasma or melanosis.

**Overdose.**
In case of overdose the events specified in the section "Side reactions" (signs of excessive amount of estrogens) may occur. These symptoms disappear at discontinuation of the treatment or reduction of the dose.

**Use during pregnancy or breast feeding.**
The product may not be used during pregnancy and breast feeding. Treatment with Oestrogel should be immediately discontinued if pregnancy is confirmed or suspected. The data of epidemiological studies have not confirmed an additional risk of occurrence of congenital defects of the fetus due to the use of estrogen at the early stages of pregnancy in case of its late diagnosis. At the same time, it should be noted that it is not required to terminate pregnancy artificially in women taking estrogens orestroprogestagens at the early stages of pregnancy in case of its late diagnosis.

**Children.** The product is not used in pediatric practice.
**Usage specifics.**

Before the beginning or before the repeated administration of hormone replacement therapy (HRT) the physician should record complete individual and family history of the female patient, to perform medical examination (including the organs of the small pelvis and breasts) with the purpose of revealing possible contraindications and taking necessary precautions at administration of the product.

During treatment it is recommended to perform regular examinations. The frequency and methods of examinations are selected individually for each patient. Women should be informed that they should inform the doctor about changes in the breasts. Studies, including mammography, should be conducted in compliance with the accepted norms and be adapted to the individual clinical needs of each patient.

If any of the below conditions occurs, took place before and/or aggravated during pregnancy or preliminary hormone therapy, the patient must be under permanent monitoring of the doctor. These conditions in some cases can recur or aggravate during treatment with Oestrogel, in particular, leiomyoma (fibromyoma) of the uterus or endometriosis in case of the history of these conditions, the factors of risk of estrogen-dependent tumors (e.g., degree I of hereditary breast cancer), arterial hypertension, mild or moderate liver diseases and hepatic adenoma, diabetes mellitus with or without lesions of vessels, cholelithiasis, migraine, systemic lupus erythematosus, epilepsy, bronchial asthma, otosclerosis.

The therapy should be discontinued at the occurrence of the following conditions: jaundice or severe liver dysfunctions, a considerable increase of blood pressure, frequent attacks of migraine-like headache.

A prolonged use of estradiol without addition of gestagenic agents may cause endometrial hyperplasia that increases the risk of developing cancer of the endometrium. Thus, in female patient with intact uterus the use of Oestrogel should be necessarily accompanied by the cyclic administration of gestagens.

During the use of Oestrogel in combination with progestagen 80-90% of the women display regular menstruation-like bleedings with the average duration of 5-6 days. Menstruation-like bleedings begin usually within 1-7 days after the last use of progestagen. "Breakthrough" bleedings and/or insignificant bloody discharges are observed during treatment in approximately 4-5% of women. Amenorrhea occurs in 3-5% of women in the first year of treatment.

Estrogens may cause retention of liquid in the body, therefore patients with dysfunction of the heart and kidneys should be under special control. Patients with renal insufficiency require particularly close monitoring, since an increase of the level of the active ingredients of Oestrogel in blood should be expected.
Changes of tolerance to glucose were observed in some patients who took estrogen/progestagen agents. Estrogen can increase sensitivity to insulin and accelerate its elimination. The blood level of glucose in the first months of HRT should be carefully monitored in patients with diabetes mellitus.

It is known about an increase of the risk of occurrence of surgically confirmed cholethiasis during menopause in the women taking estrogens.

The use of estrogens can change the results of some endocrinologic test parameters of the liver function.

Careful monitoring of the patients with hypertriglyceridemia who receive HRT is needed. There is information about several cases of a sharp increase of the triglyceride level in blood plasma during the use of estrogens by such patients that can result in the development of pancreatitis.

Estrogens elevate the level of thyroid-binding globulin (TBG) that leads to an elevation of the level of the circulating amount of hormones of the thyroid gland measured by means of protein-bound iodine, concentration of T4 (column or radioimmune method of study) or concentration of T3 (radioimmune method of study). The increase of T3 level declines, which displays the increased TBG, the concentrations of free T4 and T3 change. The serum concentrations of other binding proteins, for example, corticoid-binding globulin (CBG), globulin which binds sex hormones (GBSH) can increase that causes a rise of the concentration of circulating corticosteroids and sex steroid hormones, respectively. The concentrations of free or biologically active hormone remain unchanged. The concentration of other plasma proteins can increase (angiotensin/renin substrate, alfa-1-trypsin, ceruloplasmin).

Careful monitoring of the patients' condition is necessary in the following cases: ischemic stroke in atherosclerosis, cerebral hemorrhage, occlusion of the retinal veins, obesity due to the risk of venous thrombosis, bed rest and preparation for a planned surgery (it is desirable to discontinue treatment one month before the operation). Careful observation is required for patients with a benign tumor of the skin, prolactin-secreting tumor of the pituitary body, otospongiosis or pruritis in the anamnesis.

**Capacity to influence the reaction while driving vehicles or operating mechanisms.** The data is not available.

**Interaction with other drug products and other types of interaction.**

During concomitant use with cyclosporin, a decrease of cyclosporin elimination by the liver and an increase of the blood plasma levels of cyclosporin, creatinine and transaminases is possible.
There are references that estrogens can decrease the effect of antihypertensive and antidiabetic agents and anticoagulants. The co-administration of the agent-inducers of hepatic enzymes (barbiturates, carbamazepine, griseofulvin, phenobarbital, phenythione, primidone, ribaflavine and rifampicin) can decrease the estradiol level in blood plasma. Ritonavir and nelfinavir, although being potent inhibitors, at the co-administration with estrogens, display, on the contrary, the inducing effect. The plant agents containing the herb of Hypericum perforatum can enhance metabolism of estrogens and progestagens. At transdermal application of the product there is no effect of the "first pass" through the liver, thus, the transdermally applied estrogens and progestagens to a less extent are subject to the influence of enzyme inducers than orally administered hormones. The clinically increased metabolism of estrogens and progestagens can lead to a reduction of the effect and to a change of the character of vaginal bleeding.

**Pharmacological properties.**

*Pharmacodynamics.* The pharmacological properties are due to the presence of estradiol which is a follicular hormone. During treatment with the product the manifestations of climacteric syndrome (flushes, increased sweating, dryness of the vagina, depressed mood) significantly decrease. In women in the climacteric period the use of Oestrogel is not associated with a decrease of mineral content in the bone tissue that prevents the development of climacteric osteoporosis. The capacity to prevent osteoporosis has the individual character and is proportional to the dose of the available estrogen. At the use of 2.5 g of gel per day for 21 days the effect is ensured in about 89% of women. The transdermal route of administration allows to use natural estrogen secreted by the ovaries - estradiol-17β. This route excludes the effect of the primary pass through the liver, thereby preventing stimulation of synthesis of angiotensin, low density lipoproteins (LDLP) and some coagulating factors that decreases the risk of developing cardiovascular diseases, thromboembolisms and metabolic disorders.

*Pharmacokinetics.* At application of gel alcohol quickly evaporates. Then 10% of the applied dose, corresponding to 150 μg of estradiol, penetrates through the skin. Estradiol is retained in the subcutaneous fat and is released into the systemic circulation gradually. The estradiol level in plasma in women during the menopausal period at the use of one dose (2.5 g of gel) per day is equal to 80 pg/ml that corresponds to normal ratio of estron/estradiol in women of the reproductive age. Metabolism and elimination of estradiol at the use of Oestrogel are similar to biotransformation and elimination of natural estrogens.
**Pharmaceutical properties.**

*Main physicochemical properties:* a colorless transparent gel with odor of alcohol.

**Shelf life.** 3 years.

**Storage.**
Store at a temperature not exceeding 25°C.
Keep out of the reach of children.

**Package.**
80 mg in a tube together with the applicator-dosator placed into a carton.

**Dispensing.** Prescription medicine.

**Manufacturer.**
Besins Manufacturing Belgium, Belgium.

**Location.** 128, Groot Bijgaardenstraat, 1620 Drogenbos, Belgium.

**Date of last revision:**
Complies with the materials of the registration dossier and significant data on the use of the medicinal product.