OESTRODOSE®

FORM AND PRESENTATION
OESTRODOSE 0,06 %, gel for percutaneous application, with a dispensing metered pump (64 doses of 1,25g).

COMPOSITION QUALITATIVE ET QUANTITATIVE
- Active Ingredient: 17 β Estradiol - 0,06g for 100g of gel.
- Excipients: carbomer (980), trolamine, ethanol, purified water.

One pressure dose of the gel delivers 1.25 g, containing 0.75 mg of estradiol

THERAPEUTIC INDICATIONS
- In Hormone Replacement Therapy (HRT) for estrogen deficiency symptoms in postmenopausal women (natural or surgically induced menopause), such as vasomotor symptoms (hot flushes and sweating), trophic disorders of the genitals (vulvovaginal atrophy, dyspareunia, urinary incontinence) and psychological symptoms (sleep disturbances, asthenia, etc.) that adversely affect quality of life.
- Prevention of osteoporosis in postmenopausal women at high risk of future fractures. The efficacy of estradiol gel to prevent bone loss in postmenopausal women has been demonstrated in a double-blind placebo control study showing a significant gain of 1.2% per year in the treated group at the lumbar spine (Long-term effects of percutaneous estradiol on bone loss and bone metabolism in postmenopausal hysterectomized women.

DOSAGE AND ADMINISTRATION
Transdermal Route
OESTRODOSE 0,06 % is a with a metered dispenser pump.
Each measure from the dispenser delivers 1.25g of estradiol gel, which contains 0,75mg of estradiol.

1- <u>Menopausal Symptoms:</u>

The mean dosage is 2 pumps per day which consists in 2,5g of gel, containing 1,5mg of estradiol, for a period of 24 to 28 days/month

- **To start or continue an already initiated treatment for menopausal symptoms (the treatment can be initiated any day):** HRT should be initiated when the quality of life of the patient is altered. In all cases, an evaluation of the Benefits/risks balance should be done once every year. HRT can be continued as long as the benefits outweigh the risks.

  <u>The mean dosage is 2,5 g of gel per day = 2 pumps</u> : this dose should be adapted to the clinical response and symptoms. It can be lowered to 1 pump/day, or increased to 3 pumps/day.

a- <u>Therapeutic Schedule « with menstruation »</u>
- Day 1 to day 25 of the cycle : 2 pumps/day of OESTRODOSE (adaptable depending on cases)
- Day 14 to day 25 of the cycle: Add progesterone in non-hysterectomized women, to counter act the development of an endometrial hyperplasia, induced by estrogen.

b- <u>Therapeutic Schedule « without menstruation »</u>
- Day 1 to day 25 of the cycle : 2 pumps/day of OESTRODOSE (adaptable depending on cases)
- Day 1 to day 25 of the cycle: Combine progesterone to counter act the development of endometrial hyperplasia.

The dosage will be readapted after 2 or 3 cycles, depending on the clinical symptoms, as follows:

 Reduction of the dose in case of symptoms of excess estrogen, such as tension in the breasts, abdominal and pelvic swelling, anxiety, nervousness or aggressiveness
increase in the dose in case of symptoms of insufficient estrogen, such as persistence of hot flushes, dryness of the vagina, headaches, sleep disturbance, fatigue, and depressive tendency.

- **In case the previous treatment was a sequential HRT :**
  The cycle of the treatment must be continued before initiating treatment with OESTRODOSE 0,06%

2- <u>Prevention of osteoporosis:</u>
Controlled studies conducted with transdermal forms of estrogens have shown that the effect on prevention of bone loss varies depending on the patient but is proportional to the dose of estrogens delivered. With this gel, at the dose of 2.5 g of gel per day, 21 days out of 28, the effect of prevention of bone loss is obtained in around 89% of the women treated (against 45% under placebo).

<u>Method of administration:</u>
The gel should be applied by the patient herself to clean, dry, intact areas of skin, e.g. on the abdomen, arms, shoulders and/or inner thighs in the morning or in the evening. The area of application should be as large as possible. Gel does not need to be massaged into skin. **<u>Estradiol gel must neither be applied on the breasts nor on the mucous surfaces.</u>**
Estradiol gel should be allowed to dry for 2 minutes before covering the skin with clothing.
If the patient forgets to apply a dose, then they should apply it as soon as possible and apply the next dose at the normal time. Forgetting a dose may increase the likelihood of break-through bleeding and spotting.

CONTRAINDICATIONS
- Known, past or suspected breast cancer;
- Known or suspected estrogen-dependent malignant tumors (e.g endometrial cancer);
- Undiagnosed genital bleeding;
- Untreated endometrial hyperplasia;
- Previous idiopathic or current disease (e.g. venous thromboembolism, deep venous thrombosis, pulmonary embolism),

- Active or recent arterial thromboembolic angina, myocardial infarction, stroke);
- Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal;
- Known hypersensitivity to the active substances or to any of the excipients;
- Porphyria.

SPECIAL WARNING AND PRECAUTION OF USE

In treatment of menopausal symptoms, HRT should only be initiated if the problems are perceived from the patient as altering her quality of life. In all cases, an evaluation of the benefit/risk balance should be performed once a year. HRT should be continued as long as benefits outweigh risks.

Clinical exams and surveillance

Before initiating or restarting a Hormone Replacement Therapy (HRT), it is necessary to do a full and complete gynecological exam (Including all medical and family data), and take into consideration all contra-indications. During the whole time of the treatment, regular exams will be done on each patient; their nature and frequency depend on the patient's condition.

Women should be informed on the kind of mammary anomalies that might appear when undergoing a treatment, and should inform her doctor about those.

Special conditions requesting special surveillance

If one of the following conditions appeared, or was present before, or/and became more severe during pregnancy or a HRT, the patient must be put under close surveillance.

The following affections can reappear or become more severe during a treatment with OESTRODOSE, in particular:

- Endometriosis or uterine fibroma
- Presence or past presence of risk factors for venous-thromboembolism
- Risk Factors of estrogen-dependent tumors: example 1rst degree genetic breast cancer
- Hypertension
- Liver problems
- Diabetes
- Severe headache
- Previous endometrial hyperplasia
- Epilepsy
- Asthma

PREGNANCY AND LACTATION

Until this day, no clinical trial has shown any fetal toxicity due to estrogens, when inadvertently used in pregnant women.

UNDESIRABLE EFFECTS

Head ache, migraine, aggravation of epilepsy, mammary tension or pain, mammary hypertrophy, dysmenorrhoea, spotting, endometrial hyperplasia, benign breast tumor, uterine leiomyoma, vaginal candidosis/vaginitis, galactorrhea, rash, weight change, water retention with peripheral edema, asthenia, depression, nausea, abdominal pain, vomiting, libido modifications.

PHARMACODYNAMICS

ESTROGENS (genito-urinary system and sexual hormones)

ATC classification : G03CA03

Estradiol gel belongs to the group of natural, physiological estrogens. The active ingredient is chemically and biologically identical to human endogen estradiol. The pharmaceutical form enables the systemic administration of 17ß-estradiol by applying it to healthy skin. Estradiol gel substitutes for the loss of estrogens production in post-menopausal or ovariectomised women, and alleviates menopausal symptoms. Estrogens prevent bone loss due to menopause or ovariectomy.

STORAGE

Store at less than 25 °C

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