PATIENT LEAFLET IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986

The medicine is dispensed with a doctor's prescription only

Oestrogel

0.06% W/W

The active ingredient and its concentration:
Estradiol 0.06% W/W
Each dose of 2.5 grams contains: Estradiol 1.5 mg.
Inactive ingredients and allergens in the preparation - see section 6 "Additional information" and the "Important information about some ingredients of the medicine" section.
Read the entire leaflet carefully before using the medicine. This leaflet contains concise information about the medicine. If you have any other questions, refer to the doctor or the pharmacist.
This medicine has been prescribed for your treatment. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar.

1. What is the medicine intended for?

A hormone replacement therapy (HRT) preparation, for treatment of effects associated with estrogen deficiency in menopausal women.
Prevention of loss of bone density (osteoporosis) after menopause in women who are at high risk for osteoporotic fractures and have an intolerance or contraindication to other treatments indicated for osteoporosis prevention.
Therapeutic class: estrogens
Oestrogel replaces the estrogen produced in the body. The purpose is that the amount of estrogen in your body will be similar to the pre-menopausal amount.

2. Before using the medicine

Do not use this medicine if:

- You are sensitive to the active ingredient or to any of the additional components the medicine contains.
- You have or have ever had breast cancer, or if you are suspected of having it.
- You have or are suspected of having estrogen-dependent cancer, such as endometrial cancer.
- You have unexplained vaginal bleeding.
- You have excessive thickening of the womb lining (endometrial hyperplasia) that is not being treated.
- You have or have had a blood clot in a vein, e.g. in the legs (deep vein thrombosis) or in the lungs (pulmonary embolism).
- You have a coagulation disorder (C protein, S protein or antithrombin deficiency).
- You have or have recently had a disease due to arterial blood clot, e.g. heart attack, stroke or angina pectoris.
- You have or have had a liver disease and your liver function tests have not yet returned to normal.
- You have a disorder affecting the production of the red pigments in your blood (porphyria).

Special warnings regarding the use of the medicine

- **Before treatment with Oestrogel, tell the doctor if you have:**
  - Uterine fibrosis
  - Endometriosis - growth of the womb lining outside the womb, or a history of excessive thickening of the womb lining (endometrial hyperplasia)
  - High risk of developing blood clots
  - Risk of developing estrogen-dependent cancer (e.g., if a first-degree relative has had breast cancer)
  - High blood pressure
  - Liver problem, such as a benign tumor in the liver
  - Diabetes
  - Gallstones
  - Migraines or severe headaches
  - Systemic lupus erythematosus
  - Epilepsy
  - Asthma
  - A disease affecting the eardrum and hearing
  - Very high level of blood lipids
  - Fluid retention due to heart or kidney problems
  - Hereditary or acquired angioedema
- If you are about to undergo an operation, inform the doctor that you are taking this medicine. Stop taking the medicine 4-6 weeks before the surgery to reduce the risk of developing blood clots (see 'Blood clots and venous thrombosis' further down in this section). Consult the doctor regarding the right time to resume treatment.
- Due to the high concentration of alcohol in Oestrogel, the preparation is flammable. Do not light a cigarette or expose yourself to fire before the preparation has completely dried.

Stop using Oestrogel and refer to a doctor immediately if:

- You develop any of the conditions listed in section 2 - "Do not use this medicine if"
- You develop yellowing of the skin or of the whites of the eyes (jaundice). These may be symptoms of a liver disease
- You develop swelling in the face, tongue and/or throat and/or difficulty swallowing or hives, together with difficulty breathing, which may indicate angioedema
- A sharp rise in blood pressure has occurred
- You experience migraine-like headaches for the first time
- You have become pregnant
- You notice signs of a blood clot, such as:
  - Painful swelling and redness in the legs
  - Sudden chest pain
  - Breathing difficulties

(See 'Blood clots and venous thrombosis' further down in this section)
Note: Oestrogel is not a contraceptive. If less than 12 months have passed since your last period or if you are under 50 years of age, you may still require additional contraceptives. Contact the doctor for advice.
There is limited experience of using Oestrogel in women with premature menopause (resulting from ovarian failure or surgery), and the risks may be different. You must consult with your doctor.
Tests and follow-up
Using hormone replacement therapy involves risks that should be considered when deciding whether to start or continue treatment.
Before starting or renewing hormone replacement therapy, your doctor will ask you about your medical and family history. You may need to undergo a physical examination, including breast examination and an internal examination as necessary.
During treatment with the preparation, periodical check-ups should be performed (at least once a year), during which you should discuss with the doctor the benefits and risks involved in continuing the treatment with Oestrogel.
Periodic breast screening should be performed per your doctor's recommendation.
This medicine may alter lab tests results; therefore, before undergoing any tests, you should inform the doctor that you are using this medicine.
Risks associated with the use of hormone replacement therapy
Excessive thickening of the womb lining (endometrial hyperplasia) and endometrial cancer
Using estrogen without progestogen increases the risk for endometrial hyperplasia and endometrial cancer.
To reduce that risk in patients who have their uterus, progestogen should be added to the treatment for at least 12 days in every 28 days of treatment cycle. If you have had a hysterectomy, consult with your doctor whether you can safely use Oestrogel without progestogen supplementation.
In women who have their uterus and have not been treated with hormone replacement therapy, 5 out of 1,000 women on average will be diagnosed with endometrial cancer between the ages of 50 and 65.
In women aged 50-65 who have their uterus and are treated with an estrogen-only hormone replacement therapy, 10-60 women out of 1,000 will be diagnosed with endometrial cancer (an addition of 5-55 cases), depending on the dosage and duration of treatment.
Occasional bleeding
Bleeding is expected once a month during the treatment.
If you experience occasional bleeding or spotting beyond that monthly bleeding, which:

- continues beyond the first 6 months of treatment
- starts after more than 6 months of treatment
- continues after you have stopped using Oestrogel

refer to a doctor immediately.
Breast cancer
Combined therapy of estrogen-progestogen, and possibly also estrogen-only hormone replacement therapy, increases the risk for breast cancer. The increase in risk depends on the duration of the hormonal therapy. The increased risk becomes clear after 3 years of use. Following discontinuation of the treatment the risk decreases with time; however, it may last for 10 years or more in women with a hormone replacement therapy for more than 5 years.
For comparison
Out of 1,000 women between the ages of 50 and 54 who did not receive hormone replacement therapy, 13-17 women on average will be diagnosed with breast cancer within 5 years.
Out of 1,000 women at the age of 50 who started estrogen-only hormone replacement therapy for 5 years, there will be 16-17 cases (an addition of 0-3 cases).
Out of 1,000 women at the age of 50 who started a combined hormone replacement therapy of estrogen-progestogen for 5 years, there will be 21 cases (an addition of 4-8 cases).
Out of 1,000 women between the ages of 50-59 who did not receive hormone replacement therapy, 27 women on average will be diagnosed with breast cancer within 10 years.
Out of 1,000 women at the age of 50 who started estrogen-only hormone replacement therapy for 10 years, there will be 34 cases (an addition of 7 cases).
Out of 1,000 women at the age of 50 who started a combined hormone replacement therapy of estrogen-progestogen for 10 years, there will be 48 cases (an addition of 21 cases).
During treatment with this medicine, you should perform self breast examinations and tell your doctor if you notice:

- Skin dimpling
- Changes in the nipple
- Lumps

If you are having a mammography during treatment, inform the technician performing the test about your treatment with Oestrogel. Hormone replacement therapy can increase breast density, which may distort the results of the mammography, such that not all the masses will be found.
Ovarian cancer
Ovarian cancer is rare. Estrogen-only hormone replacement therapy and combined therapy of estrogen-progestogen have been found to slightly increase the risk for ovarian cancer. The risk for ovarian cancer is age-dependent. For example, out of 2,000 women aged 50-54 who have not been treated with hormone replacement therapy, about 2 women will be diagnosed with ovarian cancer during a 5-year period, compared with 3 women (one additional case) out of 2,000 women who have been treated with hormone replacement therapy for 5 years.
The effects of hormone replacement therapy on the heart and blood flow
Blood clots and venous thrombosis
The risk of developing venous thrombosis in women using hormone replacement therapy is 1.3-3 times higher than in women who are not using such therapy, especially during the first year of therapy.
Blood clots may be serious, and in case of a pulmonary embolism they may cause chest pain, breathing difficulties, fainting and even death.
The risk for blood clots increases with age and in the following conditions. Therefore, you should inform the doctor if you have any of the following conditions:

- You are unable to walk for a long period of time due to surgery, injury or illness (see also section 2 - 'If you are about to undergo surgery')
- Severe obesity (BMI > 30 kg/m^2)
- Coagulation disorder that requires a long-term treatment for prevention of blood clots
- Anyone in your family has had a blood clot in the legs, lungs or in another organ
- Systemic lupus erythematosus (lupus)
- Cancer

For signs of a blood clot, see section 'Stop using Oestrogel and refer to a doctor immediately if'.
For comparison, out of 1,000 women in their fifties who have not been treated with hormone replacement therapy, 4-7 women on average will have a venous blood clot during a 5-year period. Out of 1,000 women in their fifties who have been treated with a combined hormone replacement therapy of estrogen-progestogen for 5 years, there will be 9-12 cases (an addition of 5 cases). Out of 1,000 women in their fifties who have had a hysterectomy and have been treated with estrogen-only hormone replacement therapy for 5 years, there will be 5-8 cases (one additional case).
Heart disease (heart attack)
There is no evidence that hormone replacement therapy prevents heart attacks.
Women above 60 years of age who are treated with combined hormone replacement therapy of estrogen-progestogen are at a slightly higher risk of developing heart disease than women who are not using any type of hormone replacement therapy. There is no increased risk for women who have had a hysterectomy and are treated with estrogen-only hormone replacement therapy.
Stroke
The risk for a stroke is 1.5 times higher in women treated with hormone replacement therapy than in women who are not using such therapy. The risk for a stroke increases with age.
For comparison, out of 1,000 women in their fifties who have not been treated with hormone replacement therapy, 8 women on average will have a stroke in a 5-year period. Out of 1,000 women in their fifties who have been treated with hormone replacement therapy, there will be 11 cases (an addition of 3 cases) in a 5-year period.
Children
Oestrogel may accidentally pass from the skin of the patient to others. Do not allow others, especially not children, to come into contact with the skin in the area where Oestrogel is applied and cover the area, if necessary, after the gel has dried. If a child comes in contact with the area of skin where Oestrogel has been applied, wash the skin of the child with water and soap as soon as possible. As a result of estradiol transfer, young children may experience unexpected signs of puberty (such as breast buds). In most cases, the symptoms will disappear when the exposure to estradiol is discontinued. Contact the doctor in case of signs or symptoms (development of breasts or other sexual changes) in a child that may have been accidentally exposed to Oestrogel.
Other conditions
Hormone replacement therapy does not prevent memory impairment. There is limited evidence for increased risk for memory impairment in women starting hormone replacement therapy after the age of 65. Consult with your doctor.
Drug interactions
If you are taking or have recently taken other medicines, including non-prescription medicines and food supplements, tell the doctor or the pharmacist.
Especially if you are taking:

- Medicines for treatment of epilepsy (such as phenobarbital, phenytoin and carbamazepine).
- Medicines for treatment of tuberculosis (such as rifampicin, rifabutin).
- Medicines for treatment of HIV infections (such as ritonavir, nelfinavir, nevirapine, efavirenz).
- Herbal medicines containing Hypericum (St. John's Wort).
- Hormone replacement preparations may affect the activity of certain other medicines:
- A medicine for epilepsy (lamotrigine), may increase the frequency of seizures.
- Medicines for treatment of hepatitis C virus (such as combination therapy of ombitasvir/paritaprevir/ritonavir with or without dasabuvir as well as administration with glecaprevir and pibrentasvir), may cause an increase in the results of liver function in blood tests (elevation of the liver enzyme ALT) in women using combined hormonal contraception that contain ethinylestradiol. Oestrogel contains estradiol instead of ethinylestradiol. It is not known whether an elevation of the liver enzyme ALT may occur when using Oestrogel during combination therapy for hepatitis C virus.
- Skin cleansers and disinfectants, such as preparations containing benzalkonium chloride, sodium lauryl sulfate.
- Skin preparations containing alcohol, such as sunscreens or pore-minimizing/antihemorrhagic preparations.
- Preparations for skin or scalp problems, such as preparations for treatment of acne, dandruff, warts.
- Other preparations used for skin treatment which may alter the skin structure, such as anti-cancer preparations.

Pregnancy and breastfeeding
Oestrogel is intended for use in menopausal women only. If you have become pregnant while using the preparation, you must stop the treatment and refer to a doctor.
Important information about some of the ingredients of the medicine
The preparation contains alcohol.
May cause a burning sensation on damaged skin.
The product is flammable as long as it has not dried.

3. How should you use the medicine?

Always use the preparation according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and how to use the preparation.
The dosage and treatment regimen will be determined by the doctor only.
Using the medicine:

- If you have never used hormone replacement therapy or if you are starting treatment with Oestrogel after a period of time in which you were not being treated with another hormone replacement therapy, you can start the treatment on any day of your choice.
- If you are currently using hormone replacement therapy and are in the middle of a treatment cycle, finish it before starting treatment with Oestrogel.
- Oestrogel should be used by the patient herself (and not by another person).
- Do not use strong skin cleansers and disinfectants when washing the area of application.
- Avoid close contact with another person for one hour after application.
- Do not wash the skin and do not apply any other preparations to the skin for at least one hour after application.
- If the prescribed dose does not provide relief, consult with your doctor. Do not use a larger amount than what you were prescribed.

The doctor will try to find the lowest dosage that is effective for you. Consult with your doctor if you feel this dosage is too high or too low.
The generally accepted dosage is: apply once a day in the morning or evening (be sure to apply the preparation at the same time every day), preferably after taking a shower, for 24-28 consecutive days every month or for three weeks out of every four. After the break, the treatment cycle should be repeated (the dose will be adjusted by the doctor during the second and/or third cycle according to the response).
Be sure to measure the dose with the included measuring device.
Do not exceed the recommended dose.
Do not swallow.
For external use only.
Method of use:
You have been provided with a white measuring device with a groove in the middle. This groove indicates the length and width of an average dose of Oestrogel. Press the tube to release enough gel to fill the length and width of the groove. The amount of gel extracted in this manner is approximately 2.5 grams, which is the average daily dose.
Make sure that your hands and the area for application are clean, dry and unbroken.
Apply the gel over a large area of skin without massaging. Recommended areas for application: arm, shoulder or the middle inner thigh. The gel should be applied either on the outer arm and shoulder of both arms, or in the inner middle area of both thighs (the daily dose should be divided evenly for application on the chosen organ on both sides of the body).
Do not apply near the breasts and genital area.
After application, wait 5 minutes before wearing clothing over the area. Oestrogel does not stain.
If the gel is still sticky 3 minutes after application, spread the preparation over a larger area next time.
Wash your hands thoroughly after use.
If a man or a child has been exposed to Oestrogel, wash the affected area immediately with soap and water.
If you accidentally took a higher dosage, you may experience: breast tenderness, nausea and vaginal bleeding. These symptoms will resolve when treatment is discontinued or when the dosage is reduced.
If you applied an overdose or if a child swallowed this medicine by mistake, go to the doctor or the emergency room of the hospital immediately and bring the package of the medicine with you.
If you forget to take the medicine, take a dose as soon as you remember if more than 12 hours remain until the next dose, and take the next dose at the usual time.
If less than 12 hours remain until the next dose, skip the forgotten dose and take the next dose at the usual time.
Never take two doses together to compensate for the forgotten dose. If you forget a dose, you may experience bleeding or spotting.
Follow the treatment as recommended by the doctor. Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the doctor.
Do not take medicines in the dark! Check the label and the dosage every time you take the medicine.
Wear glasses if you need them.
If you have any other questions regarding the use of the medicine, consult the doctor or the pharmacist.

4. Side effects

As with any medicine, using Oestrogel may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not experience any of them.
The following conditions have been observed at a higher frequency in women treated with hormone replacement therapy than in women who have not been using such therapy:

- Breast cancer
- Excessive thickening of the womb lining (endometrial hyperplasia) or endometrial cancer
- Ovarian cancer
- Blood clots in the veins of the legs or lungs (venous thrombosis)
- Heart disease
- Stroke
- Memory impairment in women starting hormone replacement therapy after the age of 65

For more information regarding these effects, see section 2.
Side effects with unknown frequency (effects whose frequency has not yet been determined):

- Nausea
- Dizziness
- Headache
- Hair loss
- Intense itching
- Pain in the breasts
- Infection
- Pain
- Vaginal inflammation causing vaginal discharge, itching and pain

Side effects observed during the use of hormone replacement therapy in menopause:
Common side effects - side effects that occur in 1-10 out of 100 users:

- Menstrual pains
- Prolonged or heavy menstrual bleeding
- Irregular bleeding
- White or yellow vaginal discharge

Uncommon side effects - side effects that occur in 1-10 out of 1,000 users:

- Mood swings
- Migraine
- Vertigo
- Flatulence
- Increase in uterine volume
- Fungal infection in the vagina
- Feeling of weakness

Rare side effects - side effects that occur in 1-10 out of 10,000 users:

- Glucose intolerance which may affect blood sugar level
- Worsening of symptoms in women with epilepsy
- High blood pressure
- Liver function changes shown in lab tests
- Acne
- Abnormal production of breast milk
- A type of allergic reaction called anaphylactic shock (more probable in patients who have previously had an allergic reaction)

Side effects reported for other hormone replacement therapy preparations:

- Gallbladder disease
- Skin disorders:
  - Change in skin tone, especially in the face or neck, known as 'mask of pregnancy' (chloasma)
  - Red and painful skin nodules
  - Rash with target-shape reddening or sores (erythema multiforme)
- Rash
- Brown or dark skin discoloration
- Vomiting
- Abdominal pain
- Breast tenderness
- Breast enlargement
- Fluid accumulation (edema)
- Weight changes
- Increased or decreased libido
- Depression

If a side effect occurs, or if one of the side effects worsens, or if you suffer from a side effect not mentioned in the leaflet, consult with the doctor.
Side effects may be reported to the Ministry of Health by clicking on the link "Report side effects due to medicinal treatment" found on the Ministry of Health website homepage (www.health.gov.il), which will direct you to the online form for reporting side effects, or by clicking on the following link: https://sideeffects.health.gov.il/

5. How to store the medicine?

Avoid poisoning! This medicine and any other medicine must be kept in a closed place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting without an explicit instruction from the doctor.
Do not use the medicine after the expiry date (exp.) appearing on the package. The expiry date refers to the last day of that month.
Store at a temperature lower than 25°C.
The preparation may be used for up to 30 days following first opening.

6. Additional information

In addition to the active ingredient, the medicine also contains:
Ethanol, Carbomer (Carbopol 980), Trolamine (Triethanolamine), Purified water
What does the medicine look like and what are the contents of the package: An aluminum tube containing 80 grams of clear and colorless gel and a plastic measuring tool.
License holder and address: CTS Ltd., 4 Haharash St., Hod Hasharon 45240.
Name and address of the manufacturer: Besins International Laboratories, France. 3 RUE DU BOURG L'ABBE 75003 PARIS, FRANCE
This leaflet was revised in 03/2024.
Registration number of the medicine in the national drug registry of the Ministry of Health: 609326342