OESTROGEL ® Gel

Estradiol 0.06%

Please read all of the instructions carefully before using this medicine.
- Keep these instructions; you may need to read them again.
- If you have any question, if you are in doubt, ask for more information from your doctor or pharmacist.

This medicine has been prescribed for you only. Never give it someone else, even in cases of identical symptoms as this could be harmful to them.

COMPOSITION
17- β estradiol 0.06%
The other constituents are: carbomer, trolamine, ethanol, purified water.
One graduated dose corresponds to 2.5 g of gel, the equivalent of 1.5 mg estradiol.

Gel for cutaneous application, tube 80 g.
ATC classification: G03CA03
OESTROGENS- (G. genitourinary system and sex hormone).

PHARMACEUTICAL FORM
Transdermal gel.
A transparent, colourless gel with an alcoholic odour in aluminium tube, varnished inside.

INDICATION
This medicine contains a natural oestrogen. It is prescribed: Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women.

POSOLOGY AND METHOD OF ADMINISTRATION
Transdermal
The posology can be varied according to individual need.

The minimum effective dose for the treatment of post-menopausal symptoms is 1.25 g of gel per day (= 0.75 mg of oestradiol) for 21 to 28 days each month. This dose can be altered according to need and the average dose is 2.5 g of gel daily. In initiating and continuing the treatment of the symptoms of the menopause, the lowest effective dose must be used for the shortest possible duration. Continuous oestrogen treatment without a progesterone is not advisable owing to the dangers this can create for the endometrium (glandulocystic hyperplasia, dysplasia with a possible heightened risk of endometrial carcinoma); treatment must be continued for at least three consecutive weeks followed by one week during which no treatment is used and must be combined with an oral progesterone for 12 to 14 days each month. The gel can be applied from Day 1 to Day 25 of each month together with an oral progesterone. Withdrawal haemorrhage may occur during the week during which no treatment is used. Only those progestational agents that are approved for combined use with an oestrogen are recommended. Continuous treatment with an oestrogen may be indicated in women who have had a hysterectomy or where the marked symptoms of oestrogen deficiency reappear when treatment is interrupted. In this latter case, progesterone can be administered for the first 12 to 14 days of each month. Unless endometriosis was previously diagnosed, a progestational agent should not be added to the treatment of women who have had a hysterectomy.

The posology can be further adapted after 2 to 3 treatment cycles, depending on the clinical symptoms observed. More specifically:
- The dose can be decreased where signs of hyperoestrogenism are observed, such as tension in the breasts, bloating of the abdominal and pelvic area, anxiety, nervousness and aggressiveness.
- The dose can be increased where signs of hypoestrogenism are observed, such as persistent hot flushes, dryness of the vagina, headache and difficulty sleeping, asthenia and depressive tendencies.

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Do not use a double dose the next day to make up for a missed dose on the previous day. If your next dose is due in less than 12 hours, simply wait until the next dose. If your next dose is due in more than 12 hours, apply the missed dose immediately and apply the next dose at the usual time. A forgotten dose may increase the probability of spotting or bleeding.

The dose should be SPREAD OVER AS GREAT AN AREA AS POSSIBLE preferably on the forearms, arms and/or shoulders or any other large area of unbroken skin. Direct application to the breasts and the mucous membranes of the vulva and vagina should be avoided.

OESTROGEL must be applied:
- By either patient herself
- either in the morning or the evening, preferably after washing, after the same time each day

If the site of application is still sticky more than three minutes after application, the surface area covered was too small. The gel should be spread out more the next time it is applied.

When oestrogen is prescribed for a postmenopausal woman with a uterus, generally, a progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of oestrogen, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman.

Patients should be reevaluated periodically as clinically appropriate (for example at 3-month to 6-month intervals) to determine if treatment is still necessary. For woman who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding. The gel should be applied by the patients herself, not by anyone else, and skin contact, particularly with a male partner, should be avoided for one hour after application.

CONTRAINDICATION
- Breast cancer, a past history of breast cancer or suspected breast cancer.
- Known or suspected malignant oestrogen-dependent tumours (such as endometrial cancer).
- Vaginal bleeding of unknown aetiology.
- Untreated endometrial hyperplasia.
- Current or previous idiopathic venous thromboembolic accidents (deep vein thrombosis, pulmonary embolism).
- Recent or ongoing arterial thromboembolic illnesses (such as angina pectoris and myocardial infarction).
- Acute hepatic disorder or a past history of hepatic conditions, until such time as the hepatic function tests return to normal.
- Known hypersensitivity to the active ingredient or any of the excipients.
- Porphyria.
- Known or suspected pregnancy.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE
HRT is only indicated in the treatment of post-menopausal symptoms where these symptoms diminish the quality of life of the patient. In all cases, the risks and benefits of HRT must be closely studied at least once annually, and treatment must only be continued where the latter outweigh the former.

<u>Clinical examinations and monitoring:</u>
Prior to starting or resuming HRT, a complete medical history of both the patient and her family must be drawn up. Physical examinations must be carried out (in particular of the pelvic area and breasts) in view of the contraindications and precautions for use. During treatment, periodic medical examinations should be carried out. The frequency and nature of these examinations should be tailored to the patient.

All patients must be informed of the specific breast anomalies they must communicate to their doctor or nurse (see the section entitled 'Breast cancer' below). Regular check-ups that take account of the individual clinical needs of the patient and include a mammography must be carried out according to current screening practices.

Conditions that must be monitored:
If any of the conditions listed below is present, has occurred previously and/or has worsened during pregnancy or during previous hormone treatment, the patient's condition must be monitored very closely. It is important to remember that these conditions may reappear or worsen during treatment with Oestrogel. This applies in particular to:

- leiomyoma (uterine fibroma) or endometriosis;
- thromboembolic risk factors or a history thereof (see below);
- risk factors of oestrogen-dependent tumours (such as first-degree heredity for breast cancer);
- arterial hypertension;
- hepatic function disorders (such as hepatic adenoma);
- sugar diabetes with or without vascular symptoms;
- biliary lithiasis;
- migraine and severe headache;
- systemic lupus erythematosus;
- a past history of endometrial hyperplasia;
- epilepsy;
- asthma;
- otosclerosis.

In cases of simultaneous administration of a progestogen, its possible contraindications must be taken into account, i.e. pregnancy for progestogens with androgenic activity, breast, ovarian or endometrial cancer for progestogens with oestrogenic activity.

Care must be taken where there is a risk of cardiovascular, coronary and/or cerebrovascular conditions, which is greater in cases of hypertension and/or smoking. Any changes to the breasts palpated during a check-up will call for a supplementary gynaecological examination. Similarly, a doctor must be consulted where the patient experiences irregular vaginal bleeding (i.e. outside the monthly interruption to treatment), headache and visual disorders, painful swelling of the lower limbs and abdominal pain.

Reasons for immediate discontinuation of treatment
Treatment must be stopped immediately should any contraindications arise and in the event of the following:

- icterus or deterioration of hepatic function;
- a significant increase in blood pressure;
- recurrence of headaches of the migraine type;
- pregnancy or suspected pregnancy.

Endometrial hyperplasia and Endometrial Cancer:
The risk of endometrial hyperplasia and carcinoma increases when oestrogen alone is administered for protracted periods of time. Adding a progestational agent to the treatment for at least 12 days in each cycle in women whose uterus is intact significantly reduces this risk.

An increased risk of endometrial cancer has been reported with the use of unopposed oestrogen therapy in women with a uterus. The reported endometrial cancer risk among unopposed oestrogen users is about 2 to 12 times greater than in nonusers and appears dependent on duration of treatment and on oestrogen dose. Most studies show no significant increased risk associated with use of oestrogen for less than 1 year. The greatest risk appears to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more. This risk has been shown to persist for at least 8 to 15 years after oestrogen therapy is discontinued.

Withdrawal bleeding and spotting may occur during the first few months of treatment. If such bleeding occurs after treatment has been ongoing for some time or continues after discontinuation of treatment the cause must be sought and this may involve an endometrial biopsy, to exclude malignancy.

Oestrogen monotherapy can cause premalignancy or malignant transformation of residual sites of endometriosis. Adding a progestational agent to the oestrogen replacement therapy must be considered, in the treatment of women who have had a hysterectomy because of endometriosis, when the presence of residual sites of endometriosis is known.

Clinical surveillance of all women taking oestrogen plus progestin therapy is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural oestrogens results in a different endometrial risk profile than synthetic oestrogens of equivalent oestrogen dose. Adding a progestin to oestrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Breast cancer:
A randomised, controlled study involving a placebo, the study conducted by the Women's Health Initiative (WHI) and various other epidemiological studies, including the Million Women Study (MWS), have demonstrated a greater risk of breast cancer in women being treated with oestrogen, oestroprogestational combination therapies or tibolone as HRT over several years. All HRT results in a higher level of risk after several years of treatment and this risk increases with increased duration of the treatment. Nevertheless, the risk returns to its initial level over the years (5 at most) following discontinuation of treatment. However, the number of cases of breast cancer observed in that section of the WHI study which involved women who had had a hysterectomy and who were being treated with conjugated equine oestrogens was not significantly different to the number of cases observed in the placebo group. The MWS demonstrated that the relative risk of breast cancer linked to treatment with conjugated equine oestrogens (GEE) and oestradiol (E2) increased where a progestational agent was added to the therapy, whether in a sequential or continuous manner and irrespective of the type of progestational agent. No data are available to suggest any difference in the level of risk related to the method of administration. HRT, and in particular combined oestroprogestational treatment, increases the density of mammograms. This can impede x-ray detection of breast cancer.

Venous thromboembolic accidents:
HRT is associated with an increase in the relative risk of a venous thromboembolic episode (VTE), i.e. a deep vein thrombosis or pulmonary embolism. A randomised, controlled study, as well as several epidemiological studies have indicated that the risk applicable to women receiving HRT is twice to three times higher than in women not receiving HRT. The number of venous thromboembolic accidents occurring in women not receiving HRT is approximately 3 in every 1000 over a period of 5 years in the 50 to 59 age group and 8 in every 1000 women in the 60 to 69 age group.

It is estimated that the number of additional cases of VTE occurring in women who are in good health and have been treated for 5 years will be between 2 and 6 over a period of 5 years (best estimate : 4) in every 1000 patients aged between 50 and 59 and between 5 and 15 (best estimate : 9) in every 1000 patients aged between 60 and 69. VTEs are more likely to occur during the first year of HRT.

A personal or family history of VTE, severe obesity (BMI > 30 kg/m^2) and systemic lupus erythematosus (SLE) are generally recognised risk factors. There is no consensus as to the possible role played by varicose veins in the emergence of venous thrombosis.

Patients who have a past history of VTE or thrombophilia are at greater risk of developing a VTE. HRT can further increase this risk. A personal or family history of severe VTE or a history of recurring miscarriage must be investigated so as to rule out any predisposition to thrombophilia. Until such time as any thrombophilic factors have been carefully studied or treatment with an anticoagulant has been started, HRT must be considered to be contraindicated in these patients. The risks and benefits of HRT for women who are already being treated with an anticoagulant must be very closely studied. The risk of VTE may rise temporarily following prolonged immobilisation, major trauma or invasive surgery. As with all post-operative patients, scrupulous attention must be paid to the prophylactic measures used to prevent post-operative VTE. During prolonged immobilisation following elective surgery, and in particular abdominal surgery or orthopaedic surgery of the lower limbs, the suspension of HRT treatment should be considered, where possible, for four to six weeks prior to the operation, and it should be resumed only when the patient is again completely mobile. Should a VTE occur after starting treatment, treatment must be suspended. All patients must be informed of the need to contact their doctor immediately should any thromboembolic symptoms occur (i.e. painful

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swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease:
Randomised, controlled studies have not shown any cardiovascular benefit for continuous combined treatment with conjugated oestrogens and medroxyprogesterone acetate (MPA). Two major clinical studies (WHI and HERS, i.e. the Heart and Estrogen/Progestin Replacement Study) demonstrated a potentially greater risk of cardiovascular morbidity during the first year of treatment and no overall cardiovascular benefit. Only very limited data from randomised and controlled studies into cardiovascular morbidity and mortality are currently available for other types of HRT. There is therefore no certainty that these data can be applied to other forms of HRT.

Cerebrovascular accidents:
A large-scale randomised clinical study (WHI) revealed, in relation to its secondary objective, a greater risk of ischaemic CVA in women who were in good health during continuous combined treatment with conjugated oestrogens and MPA. The number of CVA occurring in women not receiving HRT is estimated at approximately 3 in every 1000 over a period of 5 years in the 50 to 59 age group and 11 in every 1000 women in the 60 to 69 age group. The number of additional cases of CVA occurring in women being treated with a combination of conjugated oestrogens and MPA over a period of 5 years is estimated at between 0 and 3 (best estimate = 1) in every 1000 women aged between 50 and 59 and between 1 and 9 (best estimate = 4) in every 1000 women aged between 60 and 69. There is no certainty that this increase also applies to other forms of HRT.

Ovarian cancer:
Some epidemiological studies have associated long-term use (at least 5 to 10 years) of oestrogen-only HRT in women who have had a hysterectomy with a greater risk of ovarian cancer. It is not known whether long-term use of a combined hormone replacement therapy results in a different risk profile to the use of oestrogen alone.

Other conditions:
Oestrogens can result in hydrosaline retention and, consequently, patients suffering from cardiac or renal dysfunction must be closely monitored. Patients suffering from terminal renal insufficiency must be closely monitored, as their circulating oestradiol levels are likely to increase.

Women who have pre-existing hypertriglyceridemia must be closely monitored when being treated with oestrogen alone or any other form of hormone replacement therapy. In some rare cases, a major increase in the plasma triglycerides has been observed and this can result in pancreatitis.

Oestrogen increases the level of thyroid-binding globulin (TBG), which can in turn lead to a rise in the total circulating levels of thyroid hormone, measured using the PBI (protein-bound iodine), T4 (spine or radioimmunoassay), or T3 (spine or radioimmunoassay) technique. The rate of T3 detected by the resins is reduced, indicating an increase in TBG. The concentrations of free T3 and T4 are not modified.

The levels of other proteins may also increase. This may apply for example to the cortisol-binding protein CBG or sexual-hormone-binding protein SHBG, which may in turn lead to an increase in the respective circulating levels of corticosteroids and sexual steroids. The free active or biological hormone concentrations remain unchanged. An increase in other plasma proteins may also be observed (angiotensinogen/renin substrate, alpha-1 antitrypsin, ceruloplasmin).

There is no conclusive proof of an increase in cognitive function. The WHI study suggests a probable increase in the risk of dementia in women beginning continuous combined treatment based on conjugated oestrogens and MPA after the age of 65. It is not known whether these observations are also applicable to younger post-menopausal women or other forms of HRT.

Dementia
In the oestrogen alone Women's Health Initiatives Memory Study (WHIMS), a substudy of WHI, a population of 2,947 hysterectomized women aged 65 to 79 years was randomized to daily conjugated oestrogens (CE 0.625 mg) or placebo. In the oestrogen plus progestin WHIMS, a population of 4,532 postmenopausal women aged 65 to 79 years was randomized to daily CE 0.625 mg plus medroxyprogesterone acetate (MPA 2.5 mg) or placebo. In the oestrogen alone substudy, after

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an average follow-up of 5.2 years, 28 women in the CE alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE alone versus placebo was 1.49 (95 percent CI, 0.83 - 2.66). The absolute risk of probable dementia for CE alone versus placebo was 37 versus 25 cases per 10,000 women-years. In the oestrogen plus progestin substudy, after an average follow-up of 4 years, 40 women in the CE/MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE/MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years. When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both substudies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women.

Gallbladder Disease
A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving oestrogens has been reported.

Hypercalcemia
Oestrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

Visual Abnormalities
Retinal vascular thrombosis has been reported in patients receiving oestrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision or a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, oestrogens should be permanently discontinued.

PRECAUTIONS

- Addition of a progestin when a woman has not had a hysterectomy
  Studies of the addition of a progestin for 10 or more days of a cycle of oestrogen administration, or daily with oestrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by oestrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins with oestrogens compared to oestrogen alone regimens. These include a possible increased risk of breast cancer, adverse effects on lipoprotein metabolism (lowering HDL, raising LDL), and impairment of glucose tolerance.

- Elevated blood pressure
  In a small number of case reports, substantial increase in blood pressure have been attributed to idiosyncratic reactions to oestrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of oestrogens on blood pressure was not seen. Blood pressure should be monitored at regular intervals with oestrogen use.

- Hypertriglyceridemia
  In patients with pre-existing hypertriglyceridemia, oestrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications. Consider discontinuation of treatment if pancreatitis or other complications develop.

- Impaired liver function and past history of cholestatic jaundice
  Oestrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past oestrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued. Topically administered oestrogen therapy avoids first pass hepatic metabolism.

- Hypothyroidism
  Oestrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Patients

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dependent on thyroid hormone replacement therapy who are also receiving oestrogens may require increased doses of their thyroid-replacement therapy. These patients should have their thyroid function monitored in order to maintain an acceptable range.

- Fluid retention
  Oestrogens may cause some degree of fluid retention. Patients who have conditions that might be influenced by this factor, such as a cardiac or renal dysfunction warrant careful observation when oestrogens are prescribed.

- Hypocalcaemia
  Oestrogens should be used with caution in individuals with severe hypocalcaemia.

- Exacerbation of endometriosis
  Endometriosis may be exacerbated with administration of oestrogens. A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with oestrogen alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

- Exacerbation of other conditions
  Oestrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic haemangiomas and should be used with caution in women with these conditions.

- Photosensitivity / Photoallergy
  Increased sensitivity to direct exposure to the sun on areas of Oestrogel application has not been evaluated.

- Effect of sunscreen application
  The effects of concomitant application of Oestrogel and a sunscreen lotion have not been evaluated.

- Alcohol-based gels are flammable
  Avoid fire, flame, or smoking until the gel has dried

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Oestrogel does not result in excessive hepatic enzyme stimulation at the standard doses. It does not have any damaging effect on the lipid balance, coagulation factors (fibrinogen, antithrombin III activity), circulating levels of renin substrate or sexual-hormone-binding globulins. It therefore does not have any hypertriglyceridemic, diabetogenic or hypertensive effect.

However, the metabolism of oestrogens can be increased by the concomitant use of enzyme inducers, in particular of the cytochrome P450 enzyme, such anticonvulsants (phenobarbital, phenytoin, carbamazepine, meprobamate, phenylbutazone) and anti-infective agents (such as rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as powerful enzyme inhibitors, act as inducers when used concomitantly with steroid hormones.

Phytotherapy preparations that contain St John's Wort (*hypericum perforatum*) can stimulate the metabolism of oestrogens and progestational agents.

Transdermal administration bypasses the first passage through the liver and the metabolism of oestrogens administered in this way is therefore less affected by enzyme inducers than that of oestrogens administered orally.

In clinical terms, an increase in the metabolism of oestrogens and progestational agents can lead to a decrease in the therapeutic effect and to changes to uterine bleeding.

PREGNANCY AND LACTATION
Pregnancy:

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Oestrogel is not indicated during pregnancy. Treatment must be suspended immediately should the patient become pregnant or should it be suspected that she is pregnant. The threat of miscarriage and suppression of lactation are not indications for oestrogen therapy.
To date, epidemiological studies have not suggested any teratogenic or foetotoxic effect in pregnant women accidentally exposed to therapeutic doses of oestrogens.

Lactation:
This medicinal product is not indicated during lactation.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Not applicable.

UNDESIRABLE EFFECTS
The table below lists all side effects, especially those observed in a maximum of 10% of patients.

System	Common side effects > 1/100; < 1/10	Rare side effects > 1/1000 ; < 1/100
Genital	Dysmenorrhea, menorrhagia, bleeding (spotting), menstrual complaints, leucorrhoea	Benign tumour of the breast, uterine polyp, increase in the volume of the uterine, fibromyoma, endometriosis, mastodynia, exacerbation of oestrogen-dependent tumours
Gastrointestinal	Abdominal pain, abdominal cramps, abdominal swelling, nausea, vomiting	
Nervous	Headache	Migraine, dizziness, sleepiness
Musculoskeletal	Muscle cramps, painful limbs	Arthralgia
Psychiatric	Nervousness, depressive syndrome	
Vascular		Superficial or deep vein thrombosis, thrombophlebitis
General		Peripheral oedema, sodium retention, feeling of bloatedness, weight change
Skin and subcutaneous tissue		Skin rash, pruritus chloasma
Hepatobiliary		Abnormal hepatic tests, hepatic adenoma, cholelithiasis
CNS	Nervousness, depression, anxiety	
Genito-urinary tract	Metrorrhagia, endometrial disorder, vaginitis pap smear suspicious, vaginal haemorrhage	
Cardiovascular system	Palpitation	
Respiratory system	Sinusitis, rhinitis	

Breast cancer
As shown in a large number of epidemiological studies as well as one randomised, controlled study involving a placebo (the WHI study), the overall risk of breast cancer increases in accordance with the duration of treatment with HRT and is also higher for recent users of HRT. For those forms of HRT which contain only oestrogen, the estimated relative risk (RR) calculated by reanalysis of the original data from 51 epidemiological studies (in which > 80% of the HRTs contained oestrogen only) and during the epidemiological study (MWS) is similar, i.e. 1.35 (95%CI, 1.21 - 1.49) and 1.30 (95%CI, 1.21-1.40) respectively.

Several epidemiological studies into combined HRT, i.e. oestrogen plus a progestational agent, have reported a higher global breast cancer risk than for oestrogen alone. The MWS demonstrated that in

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comparison to women who had never received HRT, the use of various types of oestroprogestational HRT was associated with a higher risk of breast cancer (RR = 2.00 95% CI: 1.88 - 2.12) in comparison to oestrogen alone (RR = 1.30, 95% CI: 1.21 - 1.40) and tibolone (RR = 1.45; 95% CI 1.25-1.68). The WHI study estimated the relative risk at 1.24 (95%CI 1.01 -1.54) when compared to the placebo, after 5.6 years of use of an oestroprogestational HRT (CEE + MPA) in all users. In women who have had a hysterectomy, the risk rate is 0.77 (95% CI, 0.59 -1.01) for all women treated for 6.8 years using conjugated equine oestrogen alone, in comparison to the placebo. The absolute risk, as calculated by the MWS and during the WHI study, is presented below. The MWS estimated that, on the basis of the average known incidence of breast cancer in industrialised countries:

- breast cancer will be diagnosed in approximately 32 in every 1000 women aged between 50 and 64 who are not using HRT.
- the number of additional cases over the same period of time for 1000 current or recent users of HRT will be.
- replacement therapy containing oestrogen only
  - between 0 and 3 (median value 1.5) for 5 years of treatment
  - between 3 and 7 (median value 5) for 10 years of treatment
- oestroprogestational HRT
  - between 5 and 7 (median value 6) for 5 years of treatment
  - between 18 and 20 (median value 19) for 10 years of treatment

The WHI study estimated that over a period of 5.6 years, 8 additional cases of invasive breast cancer occurring in women aged between 50 and 79 could be attributed to an oestroprogestational HRT (CEE + MPA) per 10,000 women/years.

According to the calculations based on the trial data, it is estimated that:

- for every 1000 women in the placebo group
  - approximately 16 cases of invasive breast cancer will be diagnosed over a period of 5 years;
- for every 1000 women using an oestroprogestational HRT (CEE + MPA), the number of additional cases will be
  - between 0 and 9 (median value 4) for 5 years of treatment.

The number of additional cases of breast cancer is globally similar irrespective of the age at which the patient began her HRT (in women aged between 45 and 65, see Special Warnings and Special Precaution for Use).

Endometrial cancer

In women whose uterus is intact, the risk of endometrial hyperplasia and cancer increases in accordance with the duration of oestrogen monotherapy. According to data from epidemiological studies, the best risk estimate is that applicable to women not receiving HRT : 5 endometrial cancer diagnoses can be expected in every 1000 women aged between 50 and 65. The rise in the risk of developing endometrial cancer in women using oestrogen alone in comparison to women who are not receiving HRT can be 2- to 12-fold depending on treatment duration and dose. Adding a progestational agent to an oestrogen-only therapy considerably reduces this greater risk.

The following undesirable effects have been observed during treatment with oestroprogestational agents:

- Benign and malignant oestrogen-dependent tumours, such as endometrial cancer;
- Venous thromboembolism (i.e. deep vein thrombosis of the pelvis or lower limbs and pulmonary embolism) is more frequent in women receiving HRT. For further information, see Section 4.3 "Contraindications" and 4.4 "Special warnings and Special Precautions for Use";
- Myocardial infarction and cerebrovascular accidents;
- Biliary conditions;
- Skin and subcutaneous disorders: chloasma, polymorphic erythema, erythema nodosum, vascular purpura;
- Probable increase in dementia

Other adverse reactions have been reported in association with oestrogen/ progestagen treatment:

- Genitourinary system: abnormal uterine bleeding/spotting; dysmenorrhea/pelvic pain; increase in size of uterine leiomyomata, vaginitis including vaginal candidiasis, change in

amount of cervical secretion, changes in cervical ectropion, ovarian cancer; endometrial hyperplasia; endometrial cancer.
- Breasts : tenderness, enlargement, pain; nipple discharge, galactorrhoea, fibrocystic breast changes, breast cancer.
- Cardiovascular : thrombophlebitis; increase in blood pressure.
- Gastrointestinal : nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice, pancreatitis, enlargement of hepatic haemangiomas.
- Skin : haemorrhagic eruption, loss of scalp hair, hirsutism, pruritus, rash.
- Eyes: retinal vascular thrombosis, intolerance to contact lenses.
- Central nervous system : headache, migraine, dizziness, mental depression, exacerbation of chorea, nervousness, mood disturbances, irritability, exacerbation of epilepsy, dementia.
- Miscellaneous : increase or decrease in weight, glucose intolerance, aggravation of porphyria, oedema, arthralgias, leg cramps, changes in libido, urticaria, angioedema, anaphylactoid/anaphylactic reactions, hypocalcaemia (pre-existing condition), exacerbation of asthma, increased triglycerides.

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:
Pusat Farmakovigilans/MESO Nasional Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Website: https://e-meso.pom.go.id/ADR

OVERDOSE
Symptoms
Overdosage is unlikely with transdermal applications.
Pain in the breasts or excessive production of cervical mucus may be indicative of too high a dosage, but acute overdose has not been reported and is unlikely to be a problem. Overdoses of oestrogen may cause nausea, vomiting and withdrawal bleeding. These signs disappear when the treatment is stopped or when the dose is reduced.

Treatment
There are no specific antidotes and treatment should be symptomatic.

PHARMACOLOGICAL PROPERTIES:
PHARMACODYNAMIC PROPERTIES
OESTROGENS (genitourinary system and sexual hormones)
ATC code: G03CA03

Oestrogel is a natural physiological oestrogen. The active ingredient is chemically and biologically identical to endogenous human oestradiol. It permits systemic administration of 17β-oestradiol via application to unbroken skin. It corrects a deficit in oestrogen production in postmenopausal women and women who have had an ovariectomy and soothes the symptoms of the menopause. Oestrogen prevents the loss of bone density that can occur during the menopause or following an ovariectomy. Together with a specific receptor, oestrogens form a complex which principally stimulates synthesis of DNA and proteins at the intracellular level. They have a metabolic effect on the 'target' organs.

Oestradiol is the most active oestrogen with regard to the receptors. Oestradiol is produced essentially by the ovarian follicles, from menarche through to menopause. Oestrogel will accordingly have an oestrogenic effect on the main 'target' organs, i.e. not just the ovaries, endometrium and breasts, but also the hypothalamus, hypophysis, vagina, urethra and liver. This effect is similar to that observed generally during the follicular phase. Transdermal administration of OESTROGEL bypasses the first passage through the liver thereby preventing an increase in the synthesis of angiotensinogen, VLDL lipoproteins (triglycerides) and certain coagulation factors.

Information from clinical trials

Relieving the symptoms of the menopause:
- Relief from the symptoms of the menopause is provided from the first weeks of treatment onwards.
- The profile of withdrawal haemorrhage and the extent of amenorrhoea both depend on the individual oestroprogestational posology.

PHARMACOKINETIC PROPERTIES
Over the first few hours following application of the gel (between 2 and 12 hours), the level of oestradiol reaches values that are directly proportionate lo the dose and application surface area. Serum oestradiol concentrations have been measured in trials 24 hours after daily application of 2.5 g or 5 g of gel on a surface area of 750 cm^2 of skin. These concentrations rise to an average of 75 pg/ml and 98 pg/ml respectively (interindividual variation of min. 42 to max. 122 pg/ml for 2.5 g of gel and min. 67 to max. 160 pg/ml for 5 g of gel). On average, these rates remained stable and comparable for 72 hours after one daily application of gel, and even for six consecutive cycles in other trials.

The level of oestradiol remains constant in the individual patient, even where the interval is of several months (intraindividual variation in the order of 11%). Percutaneous administration of oestradiol bypasses the first passage through the liver. A physiological ratio of circulating levels of E2 and E1 oscillating between 0.78 and 0.97 (i.e. close to one unit) is maintained and is comparable to that observed prior to the menopause. Following discontinuation of treatment, both the serum levels and concentration of conjugated oestradiol eliminated in the urine return to their base values within approximately 76 hours.

Oestradiol
The cutaneous penetration of oestradiol corresponds to approximately 10% of the dose administered. The plasma elimination half-life of oestradiol is roughly one hour. The plasma clearance rate of the metabolites vary between 640 and 900 litres/day/m^2.

The quantities of oestradiol entering the blood every 24 hours following daily cutaneous application of 2.5 g and 5 g of gel are 75 µg/day and 100 µg/day respectively. Oestradiol is principally metabolised by the liver in the form of oestriol, oestrone and their conjugates (glucuronides, sulphates), which are much less active and are mostly eliminated as glucuronides and sulphates. The metabolites also undergo an enterohepatic cycle.

PRECLINICAL SAFETY DATA
Data not available

PHARMACEUTICAL DATA
LIST OF EXCIPIENTS
Carbomer, trolamine, ethanol, purified water q.s. per 80 g.

INCOMPATIBILITIES
Not applicable.

SHELF LIFE
Three years in the sealed tubes of 80 g.
Keep out of the reach of children.
The use-by date is printed on the packaging. It follows the letter EX. And gives both the months (01 to 12) and the two last numbers of the year.

SPECIAL PRECAUTIONS FOR STORAGE
Store below 30°C.

INSTRUCTIONS FOR USE AND HANDLING
OESTROGEL must be applied:
- by the patient herself,
- either in the morning or the evening, preferably after washing, at the same time each day.

If the site of application is still sticky more than three minutes after application, the surface area covered was too small. The gel should be spread out more next time it is applied.

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PACKAGING
Box, tube @ 80 g
Reg No. DKIXXXXXXXXXX

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

Manufactured by:

BESINS MANUFACTURING BELGIUM
128, Groot Bijgaardenstraat
1620 Drogenbos – BELGIUM

Registered by:
PT. SYDNA FARMA
Jakarta – Indonesia

Date of text revision
As on approval date

Informasi untuk Pasien
Oestrogel® 0,06% (0.6 mg/g gel)
Estradiol

Bacalah seluruh informasi pada leaflet ini dengan seksama sebelum Anda mulai menggunakan obat karena leaflet ini mengandung informasi penting untuk Anda.
- Simpan leaflet ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, hubungi dokter atau apoteker Anda
- Obat ini hanya diresepkan untuk Anda. Jangan berikan kepada orang lain. Itu dapat membahayakan mereka, bahkan jika tanda-tanda penyakit mereka sama dengan Anda.
- Jika Anda mengalami efek samping, bicaralah dengan dokter atau apoteker Anda. Hal ini termasuk efek samping yang tidak disebutkan di leaflet ini. Lihat Bagian 4.

Apa isi leaflet ini:

1. Apakah itu Oestrogel® dan kegunaannya

Oestrogel® merupakan suatu *Hormone Replacement Therapy (HRT)/* Terapi Sulih Hormon. Oestrogel® mengandung hormon estrogen wanita. Oestrogel® digunakan pada wanita *pasca*menopause.

Oestrogel® digunakan untuk:
Meringankan gejala yang terjadi setelah menopause
Selama menopause, jumlah estrogen yang diproduksi oleh tubuh wanita turun. Ini dapat menyebabkan gejala seperti rasa panas pada wajah, leher dan dada ("hot flushes"). Oestrogel® mengurangi gejala-gejala ini setelah menopause. Anda akan diresepkan Oestrogel® hanya jika gejala-gejala tersebut sangat menghambat kehidupan sehari-hari Anda.

Cara kerja Oestrogel®
Oestrogel® bekerja dengan menggantikan estrogen dalam tubuh Anda sehingga Anda memiliki jumlah estrogen yang sama seperti sebelum menopause.

2. Apakah yang perlu Anda ketahui sebelum menggunakan Oestrogel®

Riwayat kesehatan dan pemeriksaan rutin
Penggunaan HRT membawa risiko yang perlu dipertimbangkan ketika memutuskan apakah akan mulai menggunakannya, atau apakah akan terus menggunakannya.
Pengalaman dalam mengobati wanita dengan menopause dini (karena kegagalan ovarium atau operasi) terbatas. Jika Anda mengalami menopause dini, risiko menggunakan HRT mungkin berbeda. Bicarakanlah dengan dokter Anda.
Sebelum Anda memulai (atau memulai kembali) HRT, dokter Anda akan bertanya tentang riwayat kesehatan Anda dan keluarga Anda. Dokter Anda mungkin memutuskan untuk melakukan

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pemeriksaan fisik. Ini mungkin termasuk pemeriksaan payudara dan/atau pemeriksaan internal, jika perlu.
Setelah Anda mulai menggunakan Oestrogel®, Anda harus mengunjungi dokter untuk pemeriksaan rutin (setidaknya setahun sekali). Pada pemeriksaan ini, diskusikan dengan dokter Anda manfaat dan risiko melanjutkan penggunaan Oestrogel®.
Lakukan skrining payudara secara teratur, sesuai anjuran dokter Anda.

Jangan gunakan Oestrogel®
Jika salah satu dari hal berikut ini berlaku untuk Anda. Jika Anda tidak yakin tentang hal-hal di bawah ini, bicarakan dengan dokter Anda sebelum menggunakan Oestrogel®.
Jangan gunakan Oestrogel®:
- Jika Anda menderita, atau pernah, atau diduga menderita **kanker payudara**,
- Jika Anda menderita, atau diduga menderita **kanker yang peka terhadap estrogen**, seperti kanker lapisan rahim (endometrium),
- Jika Anda mengalami **pendarahan vagina yang tidak dapat dijelaskan**,
- Jika Anda memiliki **penebalan berlebihan pada lapisan rahim** (hiperplasia endometrium) yang tidak diobati,
- Jika Anda mengalami atau pernah mengalami **gumpalan di pembuluh darah vena** (trombosis), seperti di kaki (trombosis vena dalam) atau paru-paru (emboli paru),
- Jika Anda memiliki **kelainan pembekuan darah** (seperti protein C, protein S, atau defisiensi antitrombin),
- Jika Anda memiliki atau baru-baru ini memiliki penyakit yang disebabkan oleh pembekuan darah di arteri, seperti **serangan jantung, stroke atau angina,**
- Jika Anda memiliki atau pernah memiliki **penyakit hati** dan tes fungsi hati Anda belum kembali normal,
- Jika Anda memiliki kelainan darah langka yang disebut "**porfiria**" yang diturunkan dalam keluarga,
- Jika Anda **alergi** (hipersensitif) terhadap estradiol atau bahan lain dari obat ini (tercantum dalam bagian 6).
- Jika Anda diketahui atau diduga hamil

Peringatan dan pencegahan
Beritahu dokter Anda jika Anda pernah mengalami salah satu dari masalah berikut sebelum Anda memulai pengobatan, karena ini dapat kembali atau menjadi lebih buruk selama penggunaan Oestrogel®. Jika demikian, Anda harus mengunjungi dokter Anda lebih sering untuk pemeriksaan:
- fibrosis di dalam rahim Anda,
- pertumbuhan lapisan rahim di luar rahim Anda (endometriosis) atau riwayat pertumbuhan lapisan rahim yang berlebihan (hiperplasia endometrium),
- peningkatan risiko pengembangan gumpalan darah (lihat “Gumpalan di pembuluh darah (trombosis)”),
- peningkatan risiko terkena kanker yang peka terhadap estrogen (seperti memiliki ibu, saudara perempuan, atau nenek yang menderita kanker payudara),
- tekanan darah tinggi,
- kelainan hati, seperti tumor hati jinak,
- diabetes,
- batu empedu,
- migrain atau sakit kepala berat,
- penyakit pada sistem kekebalan yang memengaruhi banyak organ tubuh (*Systemic Lupus Erythematosus, SLE*),
- epilepsi,
- asma,

- penyakit yang memengaruhi gendang telinga dan pendengaran (otosklerosis),
- tingkat lemak yang sangat tinggi dalam darah Anda (trigliserida),
- retensi cairan karena masalah jantung atau ginjal.

Hentikan penggunaan Oestrogel® dan segera kunjungi dokter
Jika Anda menyadari salah satu dari yang berikut ketika menggunakan HRT:
- salah satu kondisi yang disebutkan di bagian 'Jangan gunakan Oestrogel®',
- kulit atau bagian putih mata Anda menguning (*jaundice*). Ini mungkin tanda-tanda penyakit hati,
- peningkatan besar dalam tekanan darah Anda (gejalanya mungkin sakit kepala, kelelahan, pusing),
- sakit kepala mirip migrain yang terjadi untuk pertama kalinya,
- jika Anda hamil,
- jika Anda melihat tanda-tanda adanya gumpalan darah, seperti:
    - bengkak yang nyeri dan kemerahan pada kaki,
    - nyeri dada tiba-tiba
    - kesulitan bernafas,

Untuk informasi lebih lanjut, lihat 'Gumpalan darah di vena (trombosis)'.

Catatan: Oestrogel® bukan kontrasepsi. Jika kurang dari 12 bulan sejak menstruasi terakhir Anda atau Anda berusia di bawah 50 tahun, Anda mungkin masih perlu menggunakan kontrasepsi tambahan untuk mencegah kehamilan. Mintalah saran pada dokter Anda.

HRT dan kanker
Penebalan berlebihan pada lapisan rahim (hiperplasia endometrium) dan kanker pada lapisan rahim (kanker endometrium)
Menggunakan HRT dengan estrogen saja akan meningkatkan risiko penebalan berlebihan pada lapisan rahim (hiperplasia endometrium) dan kanker lapisan rahim (kanker endometrium). Menggunakan progestogen sebagai tambahan terhadap estrogen selama setidaknya 12 hari dari setiap siklus 28 hari melindungi Anda dari risiko tambahan ini. Jadi dokter Anda akan meresepkan progestogen secara terpisah jika Anda masih memiliki rahim. Jika rahim Anda telah diangkat (histerektomi), diskusikan dengan dokter Anda apakah Anda dapat menggunakan produk ini dengan aman tanpa progestogen.

Pada wanita yang masih memiliki rahim dan yang tidak menggunakan HRT, rata-rata, 5 dari 1000 akan didiagnosis dengan kanker endometrium pada usia antara 50 dan 65 tahun.
Untuk wanita berusia 50 hingga 65 tahun yang masih memiliki rahim dan menggunakan HRT dengan estrogen saja, antara 10 hingga 60 dari 1000 akan didiagnosis dengan kanker endometrium (yaitu antara 5 hingga 55 kasus tambahan), tergantung pada dosis dan durasi penggunaan.

Pendarahan yang tidak terduga
Anda akan mengalami pendarahan sebulan sekali (*withdrawal bleed*) saat menggunakan Oestrogel®. Tapi, jika Anda mengalami pendarahan tak terduga atau bercak selain pendarahan bulanan Anda, yang:
• terjadi selama lebih dari 6 bulan pertama
• dimulai setelah Anda menggunakan Oestrogel® lebih dari 6 bulan
• terjadi setelah Anda berhenti menggunakan Oestrogel®
Kunjungi dokter Anda sesegera mungkin.

Kanker payudara

Bukti menunjukkan bahwa menggunakan HRT dengan kombinasi estrogen-progestogen dan mungkin juga HRT dengan estrogen saja, meningkatkan risiko kanker payudara. Risiko tambahan tergantung pada berapa lama Anda menggunakan HRT. Risiko tambahan menjadi jelas dalam beberapa tahun. Namun, hal tersebut kembali normal dalam beberapa tahun (maksimal 5 tahun) setelah menghentikan penggunaan HRT.
Penggunaan HRT dengan estrogen saja selama 5 tahun pada wanita yang telah diangkat rahimnya menunjukkan sedikit atau tidak ada peningkatan risiko kanker payudara.

Perbandingan
Wanita berusia 50-79 tahun yang tidak menggunakan HRT, rata-rata, 9-17 dari 1000 akan didiagnosis dengan kanker payudara dalam periode 5 tahun. Untuk wanita berusia 50-79 yang menggunakan HRT kombinasi estrogen-progestogen selama lebih dari 5 tahun, akan ada 13 hingga 23 kejadian pada 1000 pengguna (yaitu 4 hingga 6 kasus tambahan).

Periksa payudara Anda secara teratur. Temui dokter Anda jika Anda melihat adanya perubahan seperti:
o lesung/cekungan di kulit
o perubahan pada puting susu
o ada benjolan yang bisa Anda lihat atau rasakan.
Selain itu, Anda disarankan untuk mengikuti program skrining mammografi. Untuk skrining mammogram, penting bagi Anda untuk memberi tahu perawat/tenaga kesehatan yang melakukan x-ray bahwa Anda menggunakan HRT, karena obat ini dapat meningkatkan kepadatan payudara Anda yang dapat mempengaruhi hasil mammogram. Ketika kepadatan payudara meningkat, mamografi mungkin tidak mendeteksi semua benjolan.

Kanker ovarium
Kanker ovarium jarang terjadi - jauh lebih jarang daripada kanker payudara. Penggunaan HRT dengan estrogen saja atau kombinasi estrogen-progestogen telah dikaitkan dengan sedikit peningkatan risiko kanker ovarium. Risiko kanker ovarium bervariasi tergantung usia. Misalnya, pada wanita berusia 50 hingga 54 tahun yang tidak menggunakan HRT, sekitar 2 dari 2000 wanita akan didiagnosis menderita kanker ovarium dalam periode 5 tahun. Untuk wanita yang telah menggunakan HRT selama 5 tahun, akan ada sekitar 3 kejadian pada 2000 pengguna (yaitu sekitar 1 kasus tambahan).

Efek HRT pada jantung dan sirkulasi
Gumpalan di pembuluh darah vena (trombosis)
Risiko **pembekuan/penggumpalan darah di pembuluh darah vena** dalah sekitar 1,3 hingga 3 kali lebih tinggi pada pengguna HRT, terutama selama tahun pertama penggunaan.
Gumpalan darah bisa menjadi serius, dan jika sampai ke paru-paru dapat menyebabkan nyeri dada, sesak napas, pingsan atau bahkan kematian.
Anda cenderung mengalami gumpalan darah di pembuluh darah seiring bertambahnya usia dan jika salah satu dari hal berikut terjadi pada Anda. Beritahu dokter Anda jika ada dari situasi berikut ini terjadi pada Anda:

- Anda tidak dapat berjalan untuk waktu lama karena operasi besar, cedera atau sakit (lihat juga bagian 3, Jika Anda perlu menjalani operasi),
- Anda sangat kelebihan berat badan (BMI> 30 kg/m^2),
- Anda memiliki masalah pembekuan darah yang membutuhkan pengobatan jangka panjang dengan obat yang digunakan untuk mencegah pembekuan darah,
- jika ada kerabat dekat Anda yang pernah memiliki gumpalan darah di kaki, paru-paru atau organ lain,
- Anda memiliki lupus erythematosus sistemik (SLE),

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- Anda menderita kanker.

Untuk tanda-tanda gumpalan darah, lihat "Hentikan penggunaan Oestrogel® dan segera kunjungi dokter".

Perbandingan
Wanita berusia 50-an yang tidak menggunakan HRT, rata-rata, selama periode 5 tahun, 4 hingga 7 dari 1000 akan diperkirakan untuk mengalami gumpalan dalam pembuluh darah.
Untuk wanita berusia 50-an yang menggunakan HRT dengan kombinasi estrogen-progestogen selama lebih dari 5 tahun, akan ada 9 hingga 12 kejadian pada 1000 pengguna (yaitu 5 kasus tambahan).
Untuk wanita berusia 50-an yang telah diangkat rahimnya dan menggunakan HRT dengan estrogen saja selama lebih dari 5 tahun, akan ada 5 hingga 8 kejadian pada 1000 pengguna (yaitu 1 kasus tambahan).

Penyakit jantung (serangan jantung)
Tidak ada bukti bahwa HRT akan mencegah serangan jantung.
Wanita berusia di atas 60 tahun yang menggunakan HRT dengan kombinasi estrogen-progestogen sedikit lebih mungkin untuk terkena penyakit jantung daripada mereka yang tidak menggunakan HRT.
Untuk wanita yang telah diangkat rahimnya dan menggunakan HRT dengan estrogen saja, tidak ada peningkatan risiko terkena penyakit jantung.

Stroke
Risiko terkena stroke adalah sekitar 1,5 kali lebih tinggi pada pengguna HRT dibandingkan pada bukan pengguna. Jumlah kasus stroke tambahan karena penggunaan HRT akan meningkat seiring bertambahnya usia.
Perbandingan
Wanita berusia 50-an yang tidak menggunakan HRT, rata-rata, 8 dari 1000 akan diperkirakan mengalami stroke selama periode 5 tahun. Untuk wanita berusia 50-an yang menggunakan HRT, akan ada 11 keajdian pada 1000 pengguna, selama periode lebih dari 5 tahun (yaitu 3 kasus tambahan).

Kondisi lain
- Penggunaan Oestrogel® dapat menyebabkan penumpukan cairan di dalam tubuh. Oleh karena itu, jika Anda memiliki gangguan fungsi jantung atau ginjal, perhatian khusus harus diberikan saat menggunakan Oestrogel®.
- Dalam beberapa kasus, kandungan lemak dalam darah dapat meningkat tajam saat menggunakan estrogen secara oral, dan dalam kasus yang jarang menyebabkan radang pankreas. Jika Anda mengalami peningkatan kadar lemak yang tajam dalam darah Anda (hipertrigliseridemia), perhatian khusus harus diberikan saat menggunakan estrogen ini.
- Pengaruh pada kadar hormon tiroid dan peningkatan kadar protein lain juga dapat terjadi pada penggunaan Oestrogel. Konsultasikanlah dengan dokter Anda.

Demensia
Penggunaan HRT tidak akan mencegah kehilangan ingatan. Ada beberapa bukti risiko kehilangan ingatan yang lebih tinggi pada wanita yang mulai menggunakan HRT setelah usia 65 tahun. Mintalah saran dokter Anda.

Penyakit Kantung Empedu
Peningkatan risiko penyakit kandung empedu pada penggunaan estrogen pada wanita postmenopause telah dilaporkan. Bicarakanlah dengan dokter Anda.

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Hiperkalsemia
Penggunaan estrogen dapat menyebabkan hiperkalsemia berat jika Anda memiliki kanker payudara dan metastasis tulang. Jika hiperkalsemia terjadi, hentikan penggunaan estrogen dan segera hubungi dokter Anda.

Gangguan Penglihatan
Segera hubungi dokter Anda jika Anda mengalami gangguan penglihatan secara tiba-tiba selama menggunakan obat ini. Dokter Anda akan memberikan saran apakah Anda dapat melanjutkan penggunaan obat ini.

Obat-obatan lainnya dan Oestrogel®
Beritahu dokter atau apoteker Anda jika Anda menggunakan, baru-baru ini menggunakan, atau mungkin menggunakan obat-obatan lain termasuk obat yang diperoleh tanpa resep, obat herbal atau produk alami.
Beberapa obat dapat mengganggu efek Oestrogel® yang mungkin menyebabkan perdarahan yang tidak teratur. Ini berlaku untuk obat-obatan berikut:

- Obat untuk **epilepsi** (seperti fenobarbital, fenitoin, dan karbamazepin).
- Obat untuk **TBC** (seperti rifampisin, rifabutin).
- Obat untuk **infeksi HIV** (seperti nevirapin, efavirenz, ritonavir dan nelfinavir).
- Produk herbal yang mengandung **St John's wort** (*Hypericum perforatum*).
- Pembersih kulit, mis. produk yang mengandung benzalkonium klorida atau sodium lauril sulfat.
- Produk kulit lainnya yang mengandung alkohol, mis. astringen atau tabir surya.
- Produk untuk mengobati gangguan kulit dan kulit kepala mis. produk untuk menyembuhkan kutil, jerawat atau ketombe.
- Obat kulit lain yang mengubah pembentukan kulit, mis. obat anti-kanker.

Tes laboratorium
Jika Anda memerlukan tes darah, beritahu dokter Anda atau staf laboratorium bahwa Anda menggunakan Oestrogel®, karena obat ini dapat memengaruhi hasil beberapa tes.

Kehamilan dan menyusui
Oestrogel® hanya digunakan pada wanita *pascamenopause*. Jika Anda hamil, hentikan penggunaan Oestrogel® dan hubungi dokter Anda.

3. Bagaimana cara menggunakan Oestrogel®

Selalu gunakan Oestrogel® persis seperti yang dikatakan dokter Anda. Periksa dengan dokter atau apoteker Anda jika Anda tidak yakin.
Menggunakan obat ini

- Jika Anda belum pernah menggunakan obat-obatan HRT lain atau Anda beralih ke Oestrogel® dari produk HRT tanpa pendarahan seperti menstruasi, Anda dapat mulai menggunakan Oestrogel® kapanpun yang sesuai untuk Anda.
- Jika saat ini Anda menggunakan HRT jenis lain di mana Anda mengalami pendarahan seperti menstruasi, habiskan obat Anda saat ini sebelum mulai menggunakan Oestrogel®.
- Jangan meminta orang lain untuk mengoleskan gel. Hanya Anda yang harus mengoleskannya.
- Jangan menggunakan pembersih kulit yang kuat saat mencuci area tempat Anda akan mengoleskan gel.
- Hindari kontak kulit yang dekat dengan pasangan Anda selama satu jam setelah pengolesan.

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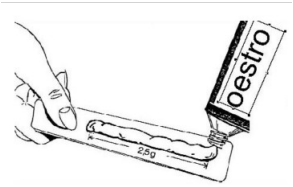
- Jangan mencuci kulit atau menggunakan produk perawatan kulit lainnya hingga setidaknya satu jam setelah pengolesan.
- Jika dosis yang diresepkan tidak memberikan efek, beritahu dokter Anda. Jangan menggunakan lebih dari dosis yang diresepkan.

Dokter Anda akan bertujuan untuk meresepkan dosis terendah untuk mengobati gejala Anda sesingkat yang diperlukan. Bicaralah dengan dokter Anda jika menurut Anda dosis ini terlalu kuat atau tidak cukup kuat.

Dosis
Oestrogel® tersedia dalam *tube*. Setiap ukuran penuh menghasilkan 2,5 g gel yang mengandung 1,5 mg estradiol. Dosis rata-rata adalah 1 ukuran penuh per hari, selama 24 hingga 28 hari per bulan.



• Wanita yang masih memiliki rahim:
Penggunaan estrogen jangka panjang tanpa penambahan progestogen meningkatkan risiko kanker endometrium pada wanita yang masih memiliki rahim. Untuk mengatasi ini perlu menggunakan kombinasi estrogen dengan progesteron setidaknya 12 hari per bulan.

Apa pun skema yang digunakan, perlu diperhatikan bahwa pengobatan ditujukan untuk penggunaan dosis efektif terkecil (rata-rata, dimulai dari 1,25 g gel per hari). Dua skema pengobatan dapat diterapkan:

Siklik:
Anda menggunakan dosis Oestrogel® selama 21 hari (3 minggu), diikuti dengan 7 hari tanpa pengobatan.
Dokter Anda mungkin juga memberi Anda pengobatan dengan hormon lain, progestogen. Anda harus menggunakan progestogen selama 12-14 hari terakhir dari 21 hari Anda menggunakan estrogen. Selama minggu ke-4, minggu di mana Anda tidak menggunakan estrogen, Anda juga tidak akan menggunakan obat yang mengandung progestogen. *Withdrawal bleeding* ('menstruasi') dapat terjadi selama periode tanpa pengobatan ini.

Sekuensial berlanjut:
Anda menggunakan Oestrogel® dosis terus menerus setiap hari (setidaknya 25 hari per bulan).
Dokter Anda mungkin juga memberikan pengobatan dengan hormon lain, progestogen. Anda harus menggunakan progestogen secara paralel, setidaknya selama 12-14 hari terakhir dalam sebulan.
Withdrawal bleeding ('menstruasi') dapat terjadi selama periode penggunaan kombinasi estrogen dan progestogen.

• Wanita tanpa rahim:
Kecuali jika Anda memiliki kelainan dimana sel-sel lapisan rahim juga ditemukan di tempat-tempat tertentu di luar rahim (endometriosis), terapi estrogen tidak boleh dikombinasikan dengan progestogen jika Anda tidak lagi memiliki rahim. Anda harus menggunakan Oestrogel® selama 12-14 hari pertama tiap bulannya.

Durasi Pengobatan

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Dokter Anda akan memberitahu Anda berapa lama Anda harus menggunakan OESTROGEL®. Penting bagi Anda untuk mematuhinya. Jangan hentikan pengobatan sebelum waktunya, diskusikan hal ini dengan dokter Anda terlebih dahulu.
Anda harus melakukan pemeriksaan kembali dengan dokter Anda secara berkala, setidaknya setiap tahun, jika Anda masih membutuhkan terapi estrogen.

Penggunaan OESTROGEL® harus dilakukan

- Di malam hari atau di pagi hari, sebaiknya setelah mandi pada waktu yang sama setiap hari.
- Dianjurkan untuk mengoleskan gel pada area kulit seluas mungkin, lebih disukai pada lengan bawah, lengan dan atau bahu atau pada area kulit yang luas.
- Hindari pemakaian pada payudara atau selaput lendir, khususnya pada mukosa vulva atau vagina.
- Jika masih terasa lengket selama lebih dari tiga menit setelah dioleskan, berarti Anda mengoleskan pada area kulit yang kecil. Ingatlah untuk mengoleskan gel pada area kulit yang lebih luas selama penggunaan selanjutnya.
- Cucilah tangan dengan air dan sabun setelah mengoleskan gel

Jika Anda yakin Oestrogel® telah dipindahkan ke orang lain
Segera cuci area kulit yang mungkin terkena dengan air dan sabun

Jika Anda menggunakan Oestrogel® lebih dari yang seharusnya
Efek dari overdosis umumnya: nyeri payudara, mual dan perdarahan vagina. Gejala-gejala ini hilang ketika pengobatan dihentikan atau dosis dikurangi. Jika Anda menggunakan dosis obat berlebihan karena tidak sengaja, segera beritahu dokter Anda.

Jika Anda lupa menggunakan Oestrogel®

- Jika lebih dari 12 jam hingga dosis berikutnya, oleskan gel segera setelah Anda ingat dan oleskan dosis berikutnya pada waktu normal.
- Jika kurang dari 12 jam hingga dosis berikutnya, lewati dosis yang terlupa dan berikan dosis berikutnya pada waktu normal.
- Jangan menggunakan dosis ganda (dua dosis sekaligus) untuk menggantikan dosis yang terlupa.

Jika Anda lupa menggunakan satu dosis, Anda mungkin mengalami pendarahan atau bercak.

Jika Anda perlu menjalani operasi
Jika Anda akan menjalani operasi, beritahu dokter Anda bahwa Anda menggunakan Oestrogel®.
Anda mungkin harus berhenti menggunakan Oestrogel® sekitar 4 hingga 6 minggu sebelum operasi untuk mengurangi risiko penggumpalan darah (lihat bagian 2, Gumpalan dalam pembuluh darah).
Tanyakan kepada dokter Anda kapan Anda dapat mulai menggunakan Oestrogel® lagi.

4. Efek samping yang mungkin terjadi
Seperti halnya penggunaan obat-obatan, obat ini dapat menyebabkan efek samping, walaupun tidak semua orang mengalaminya:
Penyakit berikut dilaporkan lebih sering pada wanita yang menggunakan HRT dibandingkan dengan wanita yang tidak menggunakan HRT:

- kanker payudara,
- pertumbuhan abnormal atau kanker pada lapisan rahim (hiperplasia endometrium atau kanker),
- kanker ovarium,
- gumpalan darah di pembuluh darah kaki atau paru-paru (tromboemboli vena),
- penyakit jantung,

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- stroke,
- kemungkinan kehilangan memori jika HRT dimulai di atas usia 65 tahun.

Untuk informasi lebih lanjut tentang efek samping ini, lihat Bagian 2.

Efek samping berikut telah dilaporkan sejak Oestrogel® dipasarkan:
Frekuensi tidak diketahui (tidak dapat diperkirakan dari data yang tersedia):
- Mual (rasa sakit di perut)
- Pusing
- Sakit kepala
- Rambut rontok (alopecia)
- Gatal-gatal hebat (pruritus)

Selama uji klinis, efek samping berikut juga telah diamati:
Frekuensi tidak diketahui (tidak dapat diperkirakan dari data yang tersedia):
- Nyeri payudara
- Infeksi
- Nyeri
- Peradangan pada vagina menyebabkan keluarnya cairan, gatal dan nyeri (vaginitis)

Efek samping yang diamati dengan penggunaan produk HRT pada menopause dilaporkan sebagai berikut:
Umum (dapat terjadi pada hingga 1 dari 10 orang):
- Nyeri menstruari
- menstruasi yang lebih berat atau lebih lama dari biasanya
- Pendarahan tidak normal atau tidak teratur
- Kelauarnya cairan putih atau kuning dari vagina

Tidak umum (dapat terjadi pada hingga 1 dari 100 orang):
- Perubahan suasana hati
- Migrain
- Vertigo
- perut kembung
- peningkatan volume uterus
- Infeksi jamur pada vagina (kandidiasis)
- Merasa lemah

Jarang (dapat terjadi pada hingga 1 dari 1000 orang):
- Intoleransi terhadap glukosa, yang dapat mempengaruhi gula darah Anda
- Jika Anda menderita epilepsi, gejala Anda mungkin memburuk
- Tekanan darah tinggi
- Tes darah menunjukkan perubahan dalam cara kerja hati
- Jerawat
- Produksi ASI yang tidak biasa
- Jenis reaksi alergi yang disebut anafilaksis (lebih mungkin jika sebelumnya Anda pernah mengalami reaksi alergi)

Efek samping berikut telah dilaporkan dengan penggunaan HRT lain:
- Penyakit kandung empedu
- Berbagai gangguan kulit:
  - perubahan warna kulit terutama wajah atau leher (chloasma)
  - nodul kemerahan pada kulit yang terasa nyeri (erythema nodosum)
  - ruam kemerahan berbentuk bulatan target atau luka (erythema multiforme)
- Ruam

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- Perubahan warna kulit menjadi coklat atau coklat gelap (melasma)
- Muntah
- Nyeri perut
- Payudara terasa lunak
- Pembesaran payudara
- Retensi cairan (edema)
- Perubahan berat badan
- Peningkatan atau penurunan hasrat seksual
- Depresi

Melaporkan efek samping
Jika Anda mengalami efek samping, bicarakan dengan dokter atau apoteker Anda. Ini termasuk kemungkinan efek samping yang tidak tercantum dalam leaflet ini.
Anda juga dapat melaporkan keluhan efek samping atau kondisi tidak nyaman tersebut secara langsung ke badan POM melalui: email pv-center@pom.go.id, website: https://e-meso.pom.go.id/ADR, atau langsung ke Industri Farmasi melalui: pv@sydna-farma.com atau pvid@besins-healthcare.com. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut mengenai keamanan obat ini

5. Bagaimana cara penyimpanan Oestrogel®
- Jauhkan obat ini dari pandangan dan jangkauan anak-anak.
- Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tercantum pada karton dan tube setelah "Exp". Tanggal kedaluwarsa mengacu pada hari terakhir bulan tersebut.
- Simpanlah pada suhu dibawah 30°C.

6. Isi kemasan dan informasi lainnya
Apa kandungan obat ini
- Zat aktifnya adalah estradiol. Ini adalah bentuk sintetik dari hormon estrogen wanita.
- Setiap papan dosis ukuran penuh 2.5 g gel mengandung 1.5 mg estradiol (dalam hemihidrat) 0.06% w/w.
- Bahan lainnya adalah: karbomer, trolamin, etanol dan air.

Seperti apa kemasan Oestrogel® dan isi kemasannya
- Gel untuk penggunaan transdermal dalam tube 80 g dengan 1 papan dosis
- Oestrogel® adalah gel transdermal yang tidak berminyak, tidak meninggalkan bekas noda, tidak berwarna, berbau alkohol.

HARUS DENGAN RESEP DOKTER

No. Reg. DKIXXXXXXXXXX

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Tanggal revisi teks:

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As on approval date

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