LEAFLET

OESTROGEL 0.06% Gel

Oestradiol

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, if you are in doubt, please ask your doctor or your pharmacist for further information.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

The active substance is oestradiol. It is contained in a gel intended for cutaneous application. A dose of 1.25 g of gel contains 0.75 mg of oestradiol.

The other ingredients (excipients) are: carbomer, trolamine, ethanol, purified water.

MARKETING AUTHORISATION HOLDER:

BESINS MANUFACTURING BELGIUM S.A.
Groot-Bijgaardenstraat, 128
B-1620 DROGENBOS
BELGIUM

MARKETING AUTHORISATION NUMBER

OESTROGEL tube: 1019 S120 F7

OESTROGEL applicator bottle: 1019 S132 F7

1. WHAT **OESTROGEL** IS AND WHAT IT IS USED FOR:

- **Pharmaceutical forms and other presentations**

- Packet containing a tube of either 30 g or 80 g of gel together with a measuring device to obtain a standard dose

- Bottle of 80 g or 2 x 100 g in a packet and complete with a dosing valve that releases exactly 1.25 g of gel

- **Pharmacotherapeutic group**

Natural physiological oestrogen
Medicine for the treatment of female hormone deficiencies

- **Therapeutic indications**

OESTROGEL belongs to a group of medicines that contain oestrogen. At the onset of the menopause or following a surgical intervention, the body no longer produces its own oestrogen. In some women, this can result in symptoms such as:

- hot flushes and mental symptoms related to the menopause, such as insomnia;
- disorders of the genital or urinary tracts related to a female hormone deficiency (reduction in volume of genital and/or urinary tissue, pain during sexual intercourse for the woman, urinary incontinence).

OESTROGEL is used to treat these symptoms where they are caused by an oestrogen deficiency in post-menopausal women and women who have undergone surgery. This medicinal product is suitable for women who have not menstruated for at least 6 months.

OESTROGEL compensates for the oestrogen deficiency and lessens the symptoms experienced.

After the menopause, oestrogen levels drop and this can result in osteoporosis (a loss of bone density).

OESTROGEL is also used to prevent osteoporosis in post-menopausal women presenting a high risk of osteoporotic bone fractures and in whom other, generally effective products cannot be used. OESTROGEL compensates for the oestrogen deficiency and reduces osteoporosis.

Very little data are available on the use of this medicine in women over the age of 65.

If your uterus has not been removed, you can use a progesterone alongside OESTROGEL for a certain number of days per month (minimum of 12 days).

2. WHAT YOU MUST KNOW BEFORE YOU USE **OESTROGEL**

Do not use OESTROGEL

- if you have or have had breast cancer or if it is suspected that you have breast cancer;
- if you have a malignant tumour that is sensitive to oestrogen or if it is suspected that you have such a tumour (e.g. a tumour of the lining of the uterus);
- if you have vaginal bleeding the cause of which is not known;
- if the lining of your uterus is growing abnormally (endometrial hyperplasia) and you have not yet been treated for this condition;
- if you have had or currently have a blood clot in any of your veins (deep vein thrombosis or pulmonary embolism) the cause of which is not known;
- if you recently had or currently have a blocked artery,or angina pectoris (heart spasms following an oxygen deficiency) or myocardial infarction;
- if you have had or currently have a liver disease, you cannot use OESTROGEL until such time as your liver function has returned to normal;
- if you have a disorder affecting the production of the red pigments of your blood (porphyria);
- if you are hypersensitive (allergic) to oestradiol or any of the other ingredients in OESTROGEL.

In cases of simultaneous administration of a progestational agent, its possible contraindications must be taken into account, i.e. pregnancy (for virilising progestational agents), cancer of the breast, ovaries or womb (for oestrogenic progestational agents).

Take special care with Oestrogel:
Before starting or resuming hormone replacement therapy (HRT) you must inform your doctor of all previous illnesses that you and close members of your family have had. You will undergo a general and gynaecological examination. During your treatment you will be asked to undergo regular check-ups, including breast checks.
Periodically – at least once annually – the advantages and disadvantages of your HRT must be studied in depth, in order to determine whether your treatment should be continued.
If any of the conditions listed below applies to you or has applied to you in the past, or worsened while you were pregnant or during previous hormone treatment, your condition must be monitored very closely. It is for these reasons that you must tell your doctor if you have had any of these conditions before you start to use Oestrogel. If you are already using Oestrogel and your condition worsens or you suffer a relapse, you must inform your doctor.
This applies in the following cases:

- a benign tumour of the uterus (uterine myoma);
- if the lining of your uterus is partially located outside the uterus itself, e.g. in the pelvic cavity (endometriosis);
- if you have suffered in the past from any coagulation disorders (thrombosis, vein thrombosis, pulmonary embolism) or if you have a high risk of developing such disorders (see HRT and thrombosis);
- if you are at particular risk of developing a tumour that is sensitive to oestrogen, for example if a member of your close family (mother, sister or daughter) has breast cancer;
- if your blood pressure is high;
- if you have a liver disease, such as a benign liver tumour (hepatic adenoma);
- if you have a sugar disorder (diabetes), whether with or without vascular symptoms;

- if you have gall stones;
- if you suffer from migraines or severe headaches;
- if you suffer from systemic lupus erythematus (a specific condition of the immune system);
- if you have abnormal growth of the lining of the uterus (endometrial hyperplasia);
- if you have epilepsy;
- if you have asthma;
- if you have otosclerosis (hereditary form of deafness).

If you are already using other medicines, you should also read the section entitled "The use of OESTROGEL in association with other medicines".

Stop using OESTROGEL immediately if:
You develop one of the conditions listed under "Do not use OESTROGEL", or one of the following situations arises:
- you contract hepatitis or your liver function deteriorates;
- your blood pressure shoots up suddenly;
- you experience a headache like a migraine for the first time;
- you become pregnant.

Important: Oestrogel does not have the same effect as the contraceptive pill.

Risks associated with OESTROGEL

Oestrogel has no harmful effects on the fatty matter in the blood (cholesterol and triglycerides), the coagulation factors, the renin substrate (linked to the risk of hypertension) or the globulins which bind to the sex hormones (signs of a hepatic overload).

Abnormal growth of the lining of the uterus (endometrial hyperplasia)
Long-term use of oestrogen without progestogen increases the risk of abnormal growth and cancer of the lining of the uterus in women whose uterus is intact. In order to reduce this risk, oestrogen must be taken together with a progesterone, for at least 12 days each month.

Occasional bleeding
During the first few months of treatment, irregular vaginal bleeding may occur (interruption haemorrhage). If such interruption haemorrhage continues for several months after treatment has started, or only starts after several months, your doctor must look for the cause of this.

Additional warning for oestrogen preparations used as a monotherapy:
An oestrogen monotherapy can cause degeneration of residual sites of endometriosis. If your uterus was removed due to endometriosis and sites of endometriosis are present, you will be prescribed additional progestogens.

HRT and breast cancer
Studies have shown an increased risk of breast cancer in women who use oestrogen or oestrogen/progestogen combinations for several years. This risk increases in accordance with the duration of HRT and would appear to drop back to its original level over the five years following the discontinuation of HRT.

Women being treated with combined HRT are at a slightly greater risk of developing breast cancer than women being treated with oestrogen alone.
Your doctor will discuss with you any abnormalities of your breasts that you may notice and will tell you when you should consult him or her for further advice.

Combined preparations can increase the density of mammograms. This can impede the x-ray detection of breast cancer.

HRT and thrombosis
Studies have shown that women who use HRT have a double to triple risk of developing vein thrombosis (formation of a blood clot in one of the veins of the legs, lungs or elsewhere in the body) in comparison to women who do not use HRT. The number of women in every 1000 who are not using HRT and who will develop vein thrombosis over a period of five years is estimated at approximately 3 in the 50 to 59 age bracket and 8 in the 60 to 69 age bracket. The number of women in every 1000 who are in good health, who are using HRT and who will develop vein thrombosis over a period of five years is estimated at approximately 4 in the 50 to 59 age bracket and 9 in the 60 to 69 age bracket. This risk is greatest during the first year of treatment with HRT.

The risk of developing vein thrombosis is greater:
- if you have previously suffered from vein thrombosis or have a coagulation disorder;
- if you are severely overweight;
- if close members of your family have experienced vein thrombosis;
- if you suffer from systemic lupus erythematus (a specific condition of the immune system).

It is not known for certain whether varicose veins lead to a greater risk of developing vein thrombosis.
If any of these situations applies to you, or has done so in the past, or if you have suffered repeated miscarriages, you will first of all be examined to ensure you do not have a predisposition to vein thrombosis. Until such time as you are examined, or treatment with an anticoagulant has been started, HRT is contraindicated. If you are already using an anticoagulant, the advantages and disadvantages of HRT must be carefully weighed up.

Furthermore, in certain situations the risk of vein thrombosis is temporarily higher, i.e.:
- following an accident
- during invasive surgery
- if you have been immobile for an extended period (for example if you have been confined to bed).

In such situations it may be necessary for you to temporarily suspend your treatment with OESTROGEL – possibly even 4 to 6 weeks prior to surgery. It is for these reasons that you must inform the physician treating you that you are using HRT if any of the above situations becomes applicable to you.

If you do develop vein thrombosis or a pulmonary embolism while you are being treated with OESTROGEL, you must stop using OESTROGEL immediately. **Notify your doctor immediately of any symptoms of vein thrombosis or pulmonary embolism, such as painful swelling of one of your legs, sudden pain in the chest and shortness of breath.**

HRT and conditions of the coronary arteries
Two large-scale studies into a specific type of HRT (conjugated oestrogen combined with medroxyprogesterone acetate) pointed to a greater risk of cardio-vascular diseases during the first year of treatment. It has not yet been determined whether this also applies to other types of medicines used in HRT.

HRT and cerebrovascular accidents
One study into a specific type of HRT (conjugated oestrogen combined with medroxyprogesterone acetate) pointed to a greater risk of cerebrovascular accidents during treatment. The number of women in every 1000 who are not using HRT and who will develop a cerebrovascular accident over a period of five years is estimated at approximately 3 in the 50 to 59 age bracket and 11 in the 60 to 69 age bracket. The number of women in every 1000 who are in good health, who are using HRT and who will develop a cerebrovascular accident over a period of five years is estimated at approximately one more in the 50 to 59 age bracket and 4 more in the 60 to 69 age bracket. It has not yet been determined whether this also applies to other types of medicines used in HRT.

HRT and ovarian cancer
Some studies suggest that women whose uterus has been removed and who use oestrogens for more than 5 to 10 years are at greater risk of developing ovarian cancer. The risk of developing ovarian cancer following long-term use of an oestrogen and progestogen combination is not known.

HRT and other conditions
- The use of OESTROGEL can lead to a build-up of fluids in the body. It is for this reason that if your heart or kidney function is in any way abnormal, you must be closely monitored while you are using OESTROGEL.
- In some cases, the fat contained in your blood may increase significantly during the use of oral oestrogens, leading in rare cases to an inflammation of the pancreas. If you have a very high level of fat in your blood (hypertriglyceridemia), you must be closely monitored while you are using oestrogens.

Using OESTROGEL with food and drink

Not applicable.

Pregnancy

You must not use OESTROGEL if you are pregnant. If you become pregnant while you are using OESTROGEL, you must stop your treatment immediately.

Ask your doctor or pharmacist for advice before taking any medicines.

Breastfeeding

You must not use OESTROGEL if you are breastfeeding.

Ask your doctor or pharmacist for advice before taking any medicines.

Driving and using machines

Not applicable

Important information about some of the ingredients of OESTROGEL

Not applicable

The use of OESTROGEL in association with **other medicines**

Some medicines diminish the effectiveness of OESTROGEL. This can also lead to irregular bleeding. This applies to the following medicines:
- medicines used to treat epilepsy (such as phenobarbital, phenytoin and carbamazepine)
- medicines used to treat tuberculosis (rifampicin, rifabutin)
- medicines used to treat infections (nevirapine, efavirenz, ritonavir, nelfinavir, rifampicin)
- plant-based medicines containing St John's Wort (hypericum perforatum), which can reduce the activity of OESTROGEL.

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those obtained with prescription.

3. HOW TO USE **OESTROGEL**

Follow these instructions closely, unless your doctor has advised you otherwise. You should check with your doctor or pharmacist if you are unsure.

- <u>If your uterus is intact:</u>
  Long-term use of oestrogen without progesterone increases the risk of endometrial cancer in women whose uterus is intact. In order to prevent this risk, oestrogen must be taken together with a progesterone for at least 12 days each month.

  Irrespective of the treatment system chosen, you must apply the smallest possible effective dose (on average from 1.25 g of gel daily, or in other words one dose). There are two possible treatment systems:

  Cyclical:

Apply one dose of OESTROGEL each day for 21 days (3 weeks), then stop for 7 days.
It is likely that your doctor will also prescribe progesterone for you. You must take your progesterone for the last 12 to 14 days of the 21 days during which you apply the oestrogen. In the fourth week, i.e. the week during which you do not apply the oestrogen, do not use any medicines containing progesterone. Some withdrawal bleeding ('menstruation') may occur during the 7 days during which you do not use any treatment.

Continuous sequential:
Apply one dose of OESTROGEL each day continuously (for at least 25 days each month). It is likely that your doctor will also prescribe another hormone, progesterone, for you. You must take the progesterone for at least the last 12 to 14 days of the month. Some withdrawal bleeding ('menstruation') may occur during the period for which you combine the oestrogen with the progestogen.

- If your uterus has been removed:
  Unless you have had an anomaly in which the cells forming the lining of your uterus appear in other places outside the uterus (endometriosis), your oestrogen treatment need not be combined with progestogens if you do not have a uterus.

If you are using OESTROGEL to treat symptoms of the menopause and you notice that the effect is either excessive or insufficient, consult your doctor.

Treatment duration

Your doctor will tell you how long you should continue to use OESTROGEL. It is important that you follow these instructions. Do not stop your treatment prematurely. Consult your doctor first.
Together with your doctor you must periodically reassess, at least once annually, whether you still require oestrogen treatment.

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. Spread the gel out more next time you apply it.

If you forget to use OESTROGEL:

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.

Effects when treatment with OESTROGEL is stopped:

Not applicable

If you use more OESTROGEL than you should:

Following an overdose, you may experience an unpleasant sensation in your breasts (painful tension) or bleeding and may feel anxious. These signs will generally disappear if you reduce the amount of gel applied.
Consult your doctor as to how you should reduce the amount of gel you apply each day.

If you use too much **OESTROGEL**, contact your doctor or pharmacist immediately or call the Poison Centre on 070 245 245.

4. POSSIBLE SIDE EFFECTS

Like all medicines, OESTROGEL can have side effects. The most common side effects of OESTROGEL are listed in the table below.

This table lists all side effects, in particular those observed in a maximum of 10% of patients.

System	Common side effects between 1/10 and 1/100	Rare side effects between 1/100 and 1/1000
Genital	Dysmenorrhea, menorrhagia, bleeding (spotting), menstrual complaints, leucorrhoea	Benign tumour of the breast, uterine polyp, increase in the volume of uterine fibromyoma, endometriosis, mastodynia, exacerbation of oestrogen-dependent tumours
Gastro-intestinal	Abdominal pain, abdominal cramps, abdominal swelling, nausea, vomiting	
Nervous	Headache	Migraine, dizziness, sleepiness
Musculo-skeletal	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

HRT can have the following side effects:

- benign and malignant tumours that are affected by oestrogen hormones, such as cancer of the lining of the uterus (endometrial cancer);
- heart attack (myocardial infarction) and cerebrovascular accidents (CVA);
- conditions affecting the gall bladder;
- skin conditions, such as:
  - chloasma (yellowy-brown patches, also known as pregnancy patches)
  - erythema multiforme (type of rash which can involve nodules, vesicles and fluid retention)
  - erythema nodosum (type of rash involving painful, blue-red nodules)
  - vascular purpura (small haemorrhages into the skin)
- symptoms of dementia

- women receiving HRT are more likely to develop vein thrombosis and pulmonary embolism than women not receiving HRT. For further information, see “Do not use OESTROGEL” and “HRT and vein thrombosis” in Section 2.
- Women receiving HRT are somewhat more likely to develop breast cancer and this risk rises with the number of years of treatment. It is estimated that of every 1000 women who are not receiving HRT, 32 will develop breast cancer in the 50 to 64 age group. It is estimated that for every 1000 women who do receive HRT over a period of 5 years or have used it recently, there will be 2 to 6 additional cases of breast cancer. Where HRT is used for 10 years this increase can be as much as 5 to 19 additional cases for every 1000 users. The number of additional cases of breast cancer is not related to the age at which HRT was started (provided it was started between the ages of 45 and 65). For further information, see “Do not use Oestrogel” and “HRT and breast cancer” in Section 2.
- Women whose uterus is intact and who are receiving HRT containing oestrogen only are more likely to develop cancer of the lining of the uterus, and this risk rises with the number of years of treatment. It is estimated that of every 1000 women who are not receiving HRT, 5 will develop uterine cancer in the 50 to 64 age group. It is estimated that for every 1000 women using oestrogen only (depending on duration and dose), approximately 10 to 60 additional cases of uterine cancer will occur. Concomitant use of a progestogen largely eliminates this risk.

If you notice any side effects which are not listed above and which you believe to be serious, inform your doctor or pharmacist.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING **OESTROGEL**

Keep out of the sight and reach of children.

The OESTROGEL sealed tubes of 30 and 80 g can be kept for three years and the OESTROGEL bottle of 80 g or 2 x 100 g can be kept for two years, in the original packaging.

The expiry date is printed on the packaging. It follows the letters EXP. and gives both the month (01 to 12) and the two last numbers of the year.

Do not use OESTROGEL beyond the expiry date shown on the packaging after the letters “exp.”.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact your doctor or pharmacist.

For all further information on this medicinal product, please contact the Marketing Authorisation Holder:

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