

NEW ZEALAND DATA SHEET

OVESTIN TABLETS

Oestriol 2mg

Presentation

Tablets 2mg - white, round, flat scored tablets with bevelled edges, coded DG above and 8 below the score line on one side, and ORGANON on the other side, and containing 2mg oestriol. Diameter 6mm, weight approximately 100mg.

Uses

Actions

Pharmacotherapeutic group: natural and semisynthetic oestrogens

ATC code: G03C A04

OVESTIN contains the natural female hormone oestriol. Unlike other oestrogens, oestriol is short acting since it has only a short term retention time in the nuclei of endometrial cells. It substitutes for the loss of oestrogen production in menopausal women and alleviates menopausal symptoms. Oestriol is particularly effective in the treatment of urogenital symptoms. In case of atrophy of the lower urogenital tract oestriol induces the normalization of the urogenital epithelium and helps to restore the normal microflora and the physiological pH in the vagina. As a result, it increases the resistance of the urogenital epithelial cells to infection and inflammation reducing vaginal complaints such as dyspareunia, dryness, itching, vaginal and urinary infections, micturition complaints and mild urinary incontinence.

Clinical trial information

- Relief of menopausal symptoms was achieved during the first weeks of treatment.
- Vaginal bleeding after treatment with OVESTIN has only rarely been reported.

Pharmacokinetics

After oral administration oestriol is rapidly and almost completely absorbed from the gastrointestinal tract. Peak plasma levels of unconjugated oestriol are reached within 1 hour of administration. After oral administration of 8mg oestriol, C_{max} is approximately 200ng/ml, C_{min} is approximately 20 ng/ml and $C_{average}$ approximately 40ng/ml.

Nearly all (90%) oestriol is bound to albumin in the plasma and in contrast with other oestrogens, hardly any oestriol is bound to sex hormone-binding globulin. The metabolism of oestriol consists mainly of conjugation and deconjugation during enterohepatic circulation. Oestriol, being a metabolic end product, is mainly excreted via the urine in the conjugated form. Only a small part ($\pm 2\%$) is excreted via the faeces, mainly as unconjugated oestriol.

Indications

Atrophy of the lower urogenital tract related to oestrogen deficiency, notably

- for the treatment of vaginal complaints such as dyspareunia, dryness and itching.
- for the prevention of recurrent infections of the vagina and lower urinary tract.
- in the management of micturition complaints (such as frequency and dysuria) and mild urinary incontinence.

Pre- and postoperative therapy in postmenopausal women undergoing vaginal surgery.

Climacteric complaints such as hot flushes and night sweating.

A diagnostic aid in case of a doubtful atrophic cervical smear.

Infertility due to cervical hostility.

Dosage And Administration

Dosage

Atrophy of the lower urogenital tract

4-8mg per day for the first weeks, followed by a gradual reduction, based on relief of symptoms, until a maintenance dosage (e.g. 1-2mg per day) is reached.

Pre- and postoperative therapy in postmenopausal women undergoing vaginal surgery

4-8mg per day in the 2 weeks before surgery; 1-2mg per day in the 2 weeks after surgery.

Climacteric complaints such as hot flushes and night sweating

4-8mg per day during the first weeks, followed by a gradual reduction. The lowest effective dosage should be used. In case of long-term treatment in women with an intact uterus, monitoring of the endometrium or, alternatively, concomitant use of a progestagen is recommended (see also

Warnings and Precautions section).

A diagnostic aid in case of a doubtful atrophic cervical smear

2-4mg per day for 7 days before taking the next smear.

Infertility due to cervical hostility

In general 1-2mg per day on days 6-15 of the menstrual cycle. However, for some patients dosages as low as 1mg per day are sufficient, whereas others may need up to 8mg per day. Therefore, the dosage should be increased each month until an optimal effect on the cervical mucus is obtained.

Administration

A missed dose should be taken as soon as remembered, unless it is more than 12 hours overdue. In the latter case the missed dose should be skipped and the next dose should be taken at the normal time. The tablets should be swallowed with some water or other drink, preferably at the same time every day. It is important that the total daily dose is taken at one time.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration of time should be used (see also **Warnings and Precautions**).

In women not taking HRT or women who switch from a continuous combined HRT product, treatment with OVESTIN may be started on any day. Women who switch from cyclic HRT regimen should start OVESTIN treatment one week after completion of the cycle.

Contraindications

- Pregnancy
- Known, past or suspected breast cancer
- Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see Warnings and Precautions)
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)
- Acute liver disease, or a history of liver disease as long as liver function tests failed to return to normal
- Known hypersensitivity to the active substances or to any of the excipients
- Porphyria
- Rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption (see **List of Excipients**).

Warnings And Precautions

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk. All current and prospective users of HRT should be advised of the risks and benefits of HRT therapy. If prescribing HRT, the potential for increased cardiovascular, thrombotic and neoplastic adverse events must be considered.

Medical Examination/Follow-Up

Before initiation or reinstating HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breast should be reported to their doctor or nurse (see **Breast Cancer** below). Investigations, including appropriate imaging tools e.g. mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions Which Need Supervision

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with OVESTIN, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- A history of, or risk factors for, thromboembolic disorders (see below)
- Risk factors for oestrogen dependent tumours, e.g. 1st degree heredity for breast cancer
- Hypertension

- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis
- Decreased glucose tolerance
- Hypercalcaemia

Reasons For Immediate Withdrawal of Therapy

Therapy should be discontinued in case a contraindication is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache
- Pregnancy

Endometrial Hyperplasia and Carcinoma

Clinical studies showed that the use of divided daily doses and long-term use of high doses of oestriol (more than 8mg daily) may lead to endometrium stimulation. In addition, one epidemiological study has shown that long-term treatment with low doses of oral oestriol may increase the risk for endometrial cancer. The risk increased with the duration of treatment and disappeared within one year after the treatment was stopped. The increased risk mainly concerned less invasive and highly differentiated tumours. In women with an intact uterus, the following precautions should be taken:

- The total daily dose should be taken at one time.
- The patient should be informed to contact a doctor if vaginal bleeding occurs. Vaginal bleeding during medication should always be investigated.
- During long-term treatment, the endometrium should be monitored at least annually.

Alternatively, a progestagen should be added, for at least 12-14 days of each calendar month.

The increased breast cancer risk associated with combined oestrogen-progestagen treatment should be considered, when making a decision to either monitor the endometrium or add a progestagen. There are no indications that treatment with oral oestriol alone increases the risk for breast cancer. Oestrogens increase the risk of endometrial cancer. Close clinical surveillance of all women taking oestrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed 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.

Breast Cancer

- HRT may increase mammographic density. This may complicate the radiological detection of breast cancer. Clinical studies reported that the likelihood of developing increased mammographic density was lower in subjects treated with oestriol than in subjects treated with other oestrogens.
- A randomized placebo-controlled trial, the Women's Health Initiative study (WHI), and epidemiological studies, including the Million Women Study (MWS), have reported an increased risk of breast cancer in women taking oestrogens, oestrogen-progestogen combinations or tibolone for HRT for several years (see **Adverse Effects**). For all HRT, an excess risk becomes apparent within a few years of use and increases with duration of intake but returns to baseline-within a few (at most five) years after stopping treatment.
- In the MWS, the relative risk of breast cancer with conjugated equine oestrogens (CEE) or oestradiol (E2) was greater when a progestogen was added, either sequentially or continuously, and regardless of type of progestogen. There was no evidence of a difference in risk between the different routes of administration.
- In the WHI study, the continuous combined conjugated equine oestrogen and medroxyprogesterone acetate (CEE +MPA) product used was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases compared to placebo.
- It is unknown whether OVESTIN carries the same risk. In a recent population-based case-control study in 3,345 women with invasive breast cancer and 3,454 controls, oestriol was

found not to be associated with an increased risk of breast cancer, in contrast to other oestrogens. However, the clinical implications of these findings are as yet unknown. Therefore, it is important that the risk of being diagnosed with breast cancer is discussed with the patient and weighed against the known benefits of HRT.

Venous Thromboembolism

- HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomized controlled trial and epidemiological studies found a 2-3 fold higher risk for users compared with non-users. For non-users it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged 60-69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate =4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate =9) per 1000 women aged 60-69 years. The occurrence of such an event is more likely in the first year of HRT than later. These studies did not include OVESTIN and, in the absence of data, it is unknown whether OVESTIN carries the same risk.
- Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see Contraindications).
- Generally recognized risk factors for VTE include use of oestrogens, older age, major surgery, prolonged immobilization, obesity (Body Mass Index >30kg/m²), pregnancy/postpartum period, systemic lupus erythematosus (SLE) and breast cancer. There is no consensus about the role of varicose veins in VTE.
- As in all postoperative patients, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilization is to follow elective surgery temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.
- In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counseling regarding its limitations (only a proportion of thrombophilic defects are identified by screening). If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g. antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.
- Patients with a history of recurrent VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.
- If OVESTIN is used for the indication 'pre-and post operative therapy....' consideration should be given to prophylactic treatment against thrombosis.
- If VTE develops after initiating OVESTIN therapy, the medicine should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary Artery Disease (CAD)

There is no evidence from randomized controlled trials of cardiovascular benefit with continuous combined conjugated oestrogens and medroxyprogesterone acetate (MPA). Two large clinical trials (WHI and HERS i.e. Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomized controlled trials examining effects in cardiovascular morbidity or mortality. Therefore, it is uncertain whether these findings also extend to other HRT products.

Ischaemic stroke

One large randomized clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated oestrogens and MPA. For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 11 per 1000 women aged 60-69 years. It is estimated that for women who use conjugated oestrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate = 1) per 1000

users aged 50-59 years and between 1 and 9 (best estimate = 4) per 1000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products.

Ovarian Cancer

Long-term (at least 5-10 years) use of oestrogen-only HRT products in hysterectomized women has been associated with an increased risk of ovarian cancer in some epidemiological studies. It is uncertain whether long-term use of combined HRT or low potency oestrogens (such as OVESTIN) confers a different risk than oestrogen-only products.

An increased risk of ovarian cancer in menopausal women taking oestrogen only replacement therapy was observed in a large US study enrolling over 40,000 women on HRT. These women were followed up for a mean duration of 13.4 years (range 1 month to 19.8 years). The increased risk of ovarian cancer in those taking oestrogen replacement therapy was 80%, RR 1.8 (95% CI, 1.1-3.0) at 10 to 19 years. This risk increased with duration of use; RR for 20 years or more years of use was 3.2 (95% CI, 1.7-5.7). This equates to approximately 3 and 8 additional cases per 10,000 women-years at these time points; (the incidence of ovarian cancer in non-users was 4.4 per 10,000 women years). This observation was most obvious in those women on long-term oestrogen replacement therapy who had a prior history of hysterectomy (defined as simple hysterectomy or hysterectomy with unilateral oophorectomy). In this subpopulation, the RR was 2.0 (95% CI, 0.96-4.3) for between 10 and 19 years of use and 3.4 (95% CI, 1.6-7.5) for 20 years or more. It is not known if the results of this study apply to Ovestin tablets as the study did not include exposure to Ovestin tablets.

Other Conditions

- Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients in OVESTIN is increased.
- Oestriol is a weak gonadotrophin inhibitor without other significant effects on the endocrine system.
- There is no conclusive evidence for improvement of cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined CEE and MPA after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products.

Use During Pregnancy And Breast-Feeding

This medicine is contraindicated during pregnancy.

If pregnancy occurs during medication with OVESTIN, treatment should be withdrawn immediately.

The results of most epidemiological studies to date relevant to inadvertent foetal exposure to oestrogens indicate no teratogenic or foetotoxic effects.

OVESTIN is not indicated during lactation. Oestriol is excreted in breast milk and may decrease milk production.

Effects on ability to drive and use machines

As far as is known OVESTIN has no effect on alertness and concentration.

Adverse Effects

From literature and safety surveillance monitoring, the following adverse reactions have been reported:

System organ class	Adverse reactions*
Reproductive system and breast disorders	Breast discomfort and pain Postmenopausal spotting Cervical discharge
Gastrointestinal disorders	Nausea
Metabolism and nutrition disorders	Fluid retention

*MedDRA version 9.1

These adverse reactions are usually transient, but may also be indicative of too high a dosage. Other adverse reactions have been reported in association with oestrogen-only and oestrogen-progestogen combined treatment. In the absence of data, it is unknown whether OVESTIN is distinct in this regard.

- Oestrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer and breast cancer. For further information see **Contraindications** and **Warnings and Precautions**
- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among HRT users than among non-users. In the absence of

data, it is unknown whether OVESTIN is distinct in this regard. For further information see **Contraindications** and **Warnings and Precautions**

- Myocardial infarction and stroke
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia over the age of 65 (see **Warnings and Precautions**)

Breast cancer risk

According to evidence from a large number of epidemiological studies and one randomised placebo-controlled trial, the Women's Health Initiative (WHI), the overall risk of breast cancer increases with increasing duration of HRT use in current or recent HRT users.

For oestrogen-only HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which >80% of HRT use was oestrogen-only HRT) and from the epidemiological Million Women Study (MWS) are similar at 1.35 (95%CI 1.21-1.49) and 1.30 (95% CI 1.21-1.40), respectively.

For oestrogen plus progestagen combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with oestrogens alone.

The MWS reported that, compared to never users, the use of various types of oestrogen-progestagen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95%CI: 1.88-2.12) than use of oestrogens alone (RR = 1.30, 95%CI: 1.21-1.40) or use of tibolone (RR = 1.45, 95%CI 1.25-1.68).

The WHI trial reported a risk estimate of 1.24 (95%CI 1.01-1.54) after 5.6 years of use of oestrogen-progestagen combined HRT (CEE + MPA) in all users compared with placebo.

The absolute risks calculated from the MWS and the WHI trial are presented below:

The MWS has estimated, from the known average incidence of breast cancer in developed countries, that:

- For women not using HRT, about 32 in every 1000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years
- For 1000 current or recent users of HRT, the number of *additional* cases during the corresponding period will be
 - For users of *oestrogen-only* replacement therapy
 - * between 0 and 3 (best estimate = 1.5) for 5 years' use
 - * between 3 and 7 (best estimate = 5) for 10 years' use
 - For users of *oestrogen plus progestagen* combined HRT
 - * between 5 and 7 (best estimate = 6) for 5 years' use
 - * between 18 and 20 (best estimate = 19) for 10 years' use

The WHI trial estimated that after 5.6 years of follow-up of women between the ages of 50 and 79 years, an *additional* 8 cases of invasive breast cancer would be due to *oestrogen-progestagen combined* HRT (CEE = MPA) per 10,000 women years.

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

- For 1000 women in the placebo group about 16 cases of invasive breast cancer would be diagnosed in 5 years
- For 1000 women who used oestrogen + progestagen combined HRT (CEE = MPA), the number of *additional* cases would be between 0 and 9 (best estimate = 4) for 5 years' use

The number of additional cases of breast cancer in women who use HRT is broadly similar for women who start HRT irrespective of age at start of use (between the ages of 45-65) (see **Warnings and Precautions** section).

Interactions

No examples of interactions between OVESTIN and other medicines have been reported in clinical practice. Although data are limited, interactions between OVESTIN and other medicinal products may occur. The following interactions have been described with use of combined oral contraceptives which may also be relevant for OVESTIN.

The metabolism of oestrogens may be increased by concomitant use of substances known to induce drug-metabolizing enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. hydantoins, barbiturates, carbamazepine), anti-infectives (e.g. griseofulvin, rifamycins, the antiretroviral agents nevirapine and efavirenz) and herbal preparations containing St John's wort (*Hypericum Perforatum*).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones.

Clinically, an increased metabolism of oestrogens may lead to decreased effectiveness of OVESTIN and changes in the uterine bleeding profile.

Oestriol may possibly increase the pharmacological effects of corticosteroids, succinylcholine, theophyllines and troleandomycin.

Overdosage

The acute toxicity of oestriol in animals is very low. Therefore, toxic symptoms are not expected to occur if several tablets are taken simultaneously. In cases of acute overdose, nausea, vomiting, and withdrawal bleeding in females may develop. No specific antidote is known. Symptomatic treatment can be given if necessary.

Pharmaceutical Precautions

List of Excipients

Potato starch, povidone, silica colloidal anhydrous, magnesium stearate, lactose monohydrate.

Store between 2°-30°C. Store in original package to protect from light and moisture.

Medicine Classification

Prescription Medicine.

Package Quantities

Nature and Contents of Container

OVESTIN tablets are packed in push through strips of PVC film backed by aluminium foil provided with heat seal coating on the side in contact with the tablets. Each push through strip contains 30 tablets. The strips are packed in cardboard boxes.

Special Precautions for Disposal

No special requirements.

Further Information

Shelf-life 3 years.

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