

NEW ZEALAND DATA SHEET

1. Ovestin Vaginal Cream 0.1%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Oestriol 1 mg/g

3. PHARMACEUTICAL FORM

Cream - a homogeneous, smooth, white to nearly white mass of creamy consistency, containing 1 mg oestriol per 1 g cream.

OVESTIN cream is filled in collapsible aluminium tubes. The tubes are provided with a polyethylene screw cap. The CE-marked applicator consists of a styrene acrylonitril barrel and a polyethylene plunger. Each tube is packed, together with an applicator in a cardboard box.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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 post-operative therapy in postmenopausal women undergoing vaginal surgery.
A diagnostic aid in case of a doubtful atrophic cervical smear.

4.2 Dose and method of administration

Dosage

OVESTIN is an oestrogen-only product that may be given to women with or without a uterus.

Atrophy of the lower urogenital tract:

1 application per day for the first weeks, followed by a gradual reduction, based on relief of symptoms, until a maintenance dosage (e.g. 1 application twice a week) is reached.

Pre- and post-operative therapy in postmenopausal women undergoing vaginal surgery:

1 application per day in the 2 weeks before surgery; 1 application twice a week in the 2 weeks after surgery.

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

1 application on alternate days in the week before taking the next smear.

Method of Administration

OVESTIN cream should be administered intravaginally by means of a calibrated applicator before retiring at night.

One application (applicator filled to the red ring mark) contains 0.5 g OVESTIN cream which corresponds to 0.5 mg oestriol.

Instructions for use for the Patient

1. Remove cap from the tube, invert it, and use the sharp point to open the tube.
2. Screw the end of the applicator onto the tube. Make sure the plunger is fully inserted into the barrel.

3. Squeeze tube slowly to fill the applicator with the cream until the plunger stops (at the red ring).
4. Unscrew applicator from tube and put the cap back on the tube.
5. To apply cream, lie down, insert end of applicator deep into the vagina.
6. Slowly push plunger all the way in until applicator is empty.
7. After use, pull plunger out of barrel beyond the point of resistance and wash both in warm, soapy water. Do not use detergents. Rinse well and dry afterwards.
DO NOT PUT THE APPLICATOR IN HOT OR BOILING WATER.
8. The applicator can be re-assembled by fully inserting the plunger into the barrel beyond the point where resistance is felt.

Discard the applicator once the tube is empty.

A missed dose should be administered as soon as remembered, unless the missed dose is noticed at the day of the next dose. In the latter case the missed dose should be skipped and the regular dosing scheme continued. Two doses must never be administered on the same day.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration of time should be used (see section 4.4 Special warnings and precautions for use).

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.

4.3 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 section 4.4 Special warnings and precautions for use)
- 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
- Hypersensitivity to the active substances or to any of the excipients
- Porphyria

4.4 Special warnings and precautions for use

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

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

In order to prevent endometrial stimulation, the daily dose should not exceed 1 application (0.5 mg oestriol) nor should this maximum dose be used for longer than several weeks.

One epidemiological study has shown that long-term treatment with low doses of oral oestriol, but not vaginal oestriol, may increase the risk for endometrial cancer. This risk increased with the duration of treatment and disappeared within one year after the treatment was terminated. The increased risk mainly concerned less invasive and highly differentiated tumours. Vaginal bleeding during medication should always be investigated. The patient should be informed to contact a doctor if vaginal bleeding occurs.

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 section 4.8 Undesirable 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 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 section 4.3, Contraindications).
- Generally recognized risk factors for VTE include use of oestrogens, older age, major surgery, prolonged immobilization, obesity (Body Mass Index > 30 kg/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 cream as the study did not look at topical oestrogens such as oestriol.

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.
- OVESTIN cream contains cetyl alcohol and stearyl alcohol. This may cause local skin reactions (e.g. contact dermatitis).
- OVESTIN is not intended for contraceptive use.

OVESTIN cream may have an unfavourable effect on latex rubber condoms. Concurrent use might increase the incidence of rupture or unnoticed slipping of the condoms.

4.5 Interaction with other medicines and other forms of interaction

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 (phenytoin), barbiturates (phenobarbital), carbamazepine), anti-infectives (e.g. griseofulvin, rifamycins (rifampicin, rifabutin), and antiretroviral agents (nevirapine, efavirenz)).

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

Herbal preparations containing St John's wort (*Hypericum Perforatum*) may induce the metabolism of oestrogens.

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

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

4.6 Fertility, pregnancy and lactation

Fertility

OVESTIN is intended for treatment in postmenopausal (naturally and surgically induced) women only.

Pregnancy

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.

Lactation

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

4.7 Effect on ability to drive and use machines

There is no information to suggest that OVESTIN affects a patient's ability to drive or operate machinery.

4.8 Undesirable effects

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

System organ class	Adverse reactions*
Metabolism and nutrition disorders	Fluid retention
Gastrointestinal disorders	Nausea
Reproductive system and breast disorders	Breast discomfort and pain Postmenopausal spotting Cervical discharge
General disorders and administration site conditions	Application site irritation and pruritus Flu-like symptoms

*MedDRA version 15.1

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 section 4.3, Contraindications and section 4.4 Special warnings and precautions for use.
- 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 section 4.3, Contraindications and section 4.4 Special warnings and precautions for use.
- 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 section 4.4 Special warnings and precautions for use)

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 trials 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 section 4.4 Special warnings and precautions for use).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions

<https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

The acute toxicity of oestriol in animals is very low. Overdosage with OVESTIN cream after vaginal administration is unlikely. However, in cases where large quantities are ingested, nausea, vomiting and withdrawal bleeding in females may occur. No specific antidote is known. Symptomatic treatment can be given if necessary.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 retention time in the nuclei of endometrial cells. It substitutes for the loss of oestrogen production in menopausal

women and alleviates menopausal symptoms. Oestrinol is particularly effective in the treatment of urogenital symptoms. In case of atrophy of the lower urogenital tract oestrinol 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.

5.2 Pharmacokinetic properties

Absorption

Intravaginal administration of oestrinol ensures optimal availability at the site of action. Oestrinol is also absorbed into the general circulation, as is shown by a sharp rise in the plasma levels of unconjugated oestrinol.

Distribution

Peak plasma levels are reached 1-2 hours after application. After vaginal application of 0.5 mg oestrinol, C_{max} is approximately 100 pg/ml, C_{min} is approximately 25 pg/ml and Coverage is approximately 70 pg/ml. After 3 weeks of daily administration of 0.5 mg vaginal oestrinol, Coverage has decreased to 40 pg/ml.

Metabolism

Nearly all (90%) oestrinol is bound to albumin in the plasma and in contrast with other oestrogens, hardly any oestrinol is bound to sex hormone-binding globulin (SHBG). The metabolism of oestrinol consists principally of conjugation and deconjugation during the enterohepatic circulation.

Elimination

Oestrinol, 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 oestrinol.

5.3 Preclinical safety data

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Octyldodecanol; Cetyl palmitate; Glycerol; Cetyl alcohol; Stearyl alcohol; Polysorbate 60; Sorbitan stearate; Lactic acid; Chlorhexidine dihydrochloride; Sodium hydroxide; Purified water.

6.2 Incompatibilities

No data available.

6.3 Shelf life

36 months from the date of manufacture.

6.4 Special precautions for storage

Store at 2°C-25°C. Do not freeze.

6.5 Nature and contents of container

Box containing a 15 g tube of cream and one applicator

6.6 Special precautions for disposal (and other handling)

No data available.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

NZ Distributor
Pharmacy Retailing (NZ) Ltd
Trading as Healthcare Logistics
Auckland, New Zealand

9. DATE OF FIRST APPROVAL

3 June 2016

10. DATE OF THE REVISION OF THE TEXT

May 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All sections revised	Update to the SPC-style format