

# New Zealand Datasheet

## Name of Medicine

VAGIFEM<sup>®</sup>

17 $\beta$ -oestradiol 25 microgram pessary

VAGIFEM<sup>®</sup> LOW

17 $\beta$ -oestradiol 10 microgram pessary

## Presentation

Vagifem is a white, film coated, biconvex pessary marked NOVO 279 on one side, blank on the other side with a diameter of 6mm, and containing 25 microgram of 17 $\beta$ -oestradiol.

Vagifem Low is a white, film coated, biconvex pessary marked NOVO 278 on one side, blank on the other side with a diameter of 6mm, and containing 10 microgram of 17 $\beta$ -oestradiol.

## Uses

### Actions

Vagifem and Vagifem Low are oestrogen preparations for intravaginal application based on the active human oestrogen oestradiol. The Vagifem and Vagifem Low modified release pessary formulations are based on a hydrophilic cellulose-derived matrix which on contact with moisture hydrates and provides a controlled release of oestradiol.

During the climacteric the decline in endogenous oestrogen production causes atrophic changes in the vaginal mucosa which may induce symptoms such as vaginal dryness, irritation and dyspareunia.

### Pharmacodynamics

Vagifem and Vagifem Low relieve the symptoms of atrophic vaginitis due to oestrogen deficiency following the menopause. Vagifem and Vagifem Low therapy reverse the atrophic changes due to oestrogen deficiency found in the affected post-menopausal vagina. The active ingredient, synthetic 17 $\beta$ -oestradiol, is chemically and biologically identical to endogenous human oestradiol.

Endogenous 17 $\beta$ -oestradiol induces and maintains the primary and secondary female sexual characteristics. The biological effect of 17 $\beta$ -oestradiol is carried out through a number of specific oestrogen receptors. The steroid receptor complex is bound to the cell's DNA and induces synthesis of specific proteins.

Maturation of the vaginal epithelium is dependant upon oestrogen. Oestrogen increases the number of superficial and intermediate cells as compared to basal cells.

Oestrogen keeps pH in the vagina down to around 4.5 which enhances normal bacterial flora, *Lactobacillus döderlein* predomination.

### Pharmacokinetics

The modified release pessary formulations of Vagifem and Vagifem Low are based on a hydrophilic cellulose-derived matrix which hydrates on contact with moisture to give a controlled release of the soluble oestradiol. Once the pessary is in place, it adheres to the vaginal mucosa. The polymer selected for the gel matrix hydrates quickly so that a gel layer is formed before the contents of the pessary begin to dissolve. Soluble oestradiol is gradually released from the hydrophilic matrix.

Oestrogen drug products are well absorbed through the skin, mucous membranes, and the gastrointestinal tract. The vaginal delivery of oestrogens circumvents first-pass metabolism. After treatment with Vagifem and Vagifem Low, marginal elevations of plasma oestradiol and its metabolites, as well as (Vagifem only) minor suppression of pituitary gonadotrophins, have been observed. This indicates that some absorption of oestradiol occurs. Absorption is low as shown in the study described below.

A 12 week, single-centre randomised, open label, multiple dose, parallel-group trial was conducted to evaluate the extent of systemic absorption of oestradiol from Vagifem and Vagifem Low. Subjects were randomized 1:1 to receive either 25 micrograms E2 (Vagifem) or 10 micrograms E2 (Vagifem Low). Plasma levels of oestradiol (E2), oestrone (E1) and oestrone sulfate (E1S) were determined at Day -1 (pre-dose), Day 1 (after 1st dosing), Day 14 (after 14 days of once-daily dosing), Day 82 (pre-dose after 10 weeks twice-weekly treatment) and Day 83 (post-dose after 10 weeks twice-weekly treatment). The primary bioavailability endpoint of the clinical trial was  $AUC_{(0-24)}$  for plasma E2 levels (see Table 1): this parameter indicated higher systemic oestradiol levels for Vagifem and Vagifem Low as compared to baseline on treatment days 1, 14 and 83. However, average plasma E2 concentrations ( $C_{ave(0-24)}$ ) at all timepoints overall remained below 20 pg/ml (below approx. 73.4 pmol/L) and therefore within the normal postmenopausal range. The data from day 82 indicate that in the long term, systemic oestradiol levels do not accumulate during twice weekly maintenance therapy (see Table 1).

Table 1: Values of PK parameters from plasma oestradiol (E2) concentrations: Study VAG-1850

	<b>Vagifem Low (10 micrograms E2)</b>		<b>Vagifem (25 micrograms E2)</b>	
	$AUC_{(0-24)}$ pg.h/mL (geom. mean)	$C_{ave(0-24)}$ pg/mL (geom. mean) [% patients > 20 pg/mL (> approx. 73.4 pmol/L)]	$AUC_{(0-24)}$ pg.h/mL (geom. mean)	$C_{ave(0-24)}$ pg/mL (geom. mean) [% patients > 20 pg/mL (> approx. 73.4 pmol/L)]
Day -1	75.65	3.15	96.66	4.03
Day 1	225.35	9.39 [0%]	476.14	19.84 [54%]
Day 14	157.47	6.56 [0%]	438.87	18.29 [37%]
Day 82	44.95	1.87 [0%]	48.13	2.01 [0%]
Day 83	111.41	4.64 [0%]	225.94	9.41 [15%]

The levels of oestrone seen during 12 weeks of Vagifem or Vagifem Low administration do not show any accumulation of oestrone.

Oestrogen metabolites are primarily excreted in the urine as glucuronides and sulfates.

### Indications

Vagifem and Vagifem Low are indicated for the treatment of atrophic vaginitis due to oestrogen deficiency in postmenopausal women.

Vagifem and Vagifem Low are not intended for children or males.

### Dosage and Administration

Vagifem and Vagifem Low may be used in women with or without an intact uterus.

Vagifem and Vagifem Low are administered deep intravaginally using the applicator.

Initial dose: 1 modified release pessary daily for 2 weeks

Maintenance dose: 1 modified release pessary twice a week.

If a dose is forgotten, it should be taken as soon as the patient remembers. A double dose should be avoided.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see Warnings and Precautions) should be used. Patient review should occur 3-6 months after treatment initiation. Reassessment of risks and benefits should occur no less frequently than annually.

There are currently no data to provide guidance on switching between Vagifem and Vagifem Low presentations.

## **Contraindications**

- Known, suspected or past history of carcinoma of the breast
- Known, suspected or past history of oestrogen dependent neoplasia, e.g. endometrial carcinoma or other hormone dependent tumour
- Abnormal genital bleeding of unknown aetiology
- Known or suspected pregnancy
- 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 previous arterial thromboembolic disease (e.g. angina, myocardial infarction)
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal
- Porphyria
- Known hypersensitivity to the active substance or to any of the excipients.

## **Warnings and Precautions**

Hormone Replacement Therapy (HRT) should only be initiated for the short-term treatment of postmenopausal symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken.

Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited.

### Medical examination/follow-up

Before initiating or reinstating of therapy with Vagifem or Vagifem Low it is advisable to undertake a thorough examination to exclude any possibility of genital or mammary tumours. 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. Vaginal infections should be treated before initiation of Vagifem or Vagifem Low therapy.

During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman, but no less frequently than annually. Women should be advised what changes in their breasts should be reported to their doctor or nurse. 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. Persistent or recurring vaginal bleeding should be investigated.

The pharmacokinetic profiles of Vagifem and Vagifem Low show that there is very low systemic absorption of oestradiol during treatment (see Pharmacokinetics), however being HRT products the following need to be considered, especially for long term or repeated use of these products

### 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 oestrogen treatment. Patients with the following conditions should be monitored frequently and if any of the conditions worsen, Vagifem or Vagifem Low treatment should be withdrawn:

- Leiomyoma (uterine fibroids) or endometriosis
- Liver disorders (e.g. liver adenoma)
- Cholelithiasis
- Risk factors for oestrogen dependent tumours, e.g. 1<sup>st</sup> degree heredity for breast cancer
- Risk factors for thromboembolic disorders (see below)
- Haemoglobinopathies or sickle-cell anaemia
- Epilepsy
- Migraine or severe headache
- Diabetes mellitus with or without vascular involvement
- Asthma
- Cardiac dysfunction
- Hypertension
- Systemic lupus erythematosus (SLE)
- A history of endometrial hyperplasia (see below)
- Otosclerosis

### Reasons for immediate withdrawal of therapy:

Therapy should be discontinued upon discovery of a contraindication and in the following situations

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

### Genotoxicity

There is limited evidence available in the literature suggesting that oestradiol may be weakly genotoxic. No evidence could be found for an increase in the rate of gene mutation in bacterial or mammalian cells, but there was some evidence for the induction of chromosomal aberrations and aneuploidy and an increased incidence of sister chromatid exchanges (indicative of DNA damage) in mammalian cells. None of these effects were induced by oestradiol in human lymphocyte cultures. Importantly, there was no evidence of clastogenicity in rodent bone marrow micronucleus assays.

### Carcinogenicity

Supra-physiological doses of oestradiol have been associated with the induction of tumours in oestrogen-dependent target organs in all rodent species tested. The relevance of these findings with respect to humans has not been established.

### Endometrial hyperplasia and carcinoma

Women with an intact uterus with abnormal bleeding of unknown aetiology or women with an intact uterus who have previously been treated with unopposed oestrogens should be examined with special care in order to exclude hyperstimulation/malignancy of the endometrium before initiation of treatment with Vagifem or Vagifem Low.

There is some evidence that obesity and possibly hypertension or diabetes mellitus are predisposing factors to endometrial carcinoma. In view of this, special care should be taken in the presence of these conditions and also if a family history of endometrial carcinoma is

present. Endometrial hyperplasia (atypical or adenomatous) often precedes endometrial cancer. The risk of endometrial cancer after treatment with oral unopposed oestrogens is dependent on both duration of treatment and on oestrogen dose. In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among systemic oestrogen-only users varies from 2- to 12-fold compared with non-users, depending on both duration of treatment and on oestrogen dose. After stopping treatment, risk may remain elevated for at least 10 years.

Endometrial safety of long-term (more than one year) or repeated use of local vaginally administered oestrogen is uncertain. Therefore, if repeated, treatment should be reviewed at least annually, with special consideration given to any symptoms of endometrial hyperplasia or carcinoma.

As a general rule, oestrogen replacement therapy should not be prescribed for longer than one year without another physical, including gynaecological, examination being performed.

If bleeding or spotting appears at any time during therapy, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

The woman should be advised to contact her doctor in case bleeding or spotting occurs during treatment with Vagifem or Vagifem Low.

Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore caution is advised when using these products in women who have undergone hysterectomy because of endometriosis, especially if they are known to have residual endometriosis.

### Breast Cancer

There is a need for caution in prescribing oestrogens to women with a strong family history of breast cancer or who have breast nodules. The overall evidence suggests an increased risk of breast cancer in women taking combined oestrogen-progestagen and possibly also oestrogen-only HRT, that is dependent on the duration of taking HRT.

Observational studies in hysterectomised women using oestrogen-only HRT have mostly reported a small increase in risk of having breast cancer diagnosed that is substantially lower than found in users of oestrogen-progestagen combinations. The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment.

A relationship between breast cancer risk and low dose local vaginal oestrogen therapy is uncertain.

HRT, especially oestrogen-progestagen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

### Ovarian cancer

Ovarian cancer is much rarer than breast cancer. Long-term (at least 5-10 years') use of systemic oestrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer. Some studies including the WHI trial suggest that the long-term use of combined HRTs may confer a similar or slightly smaller risk (see 'Adverse Effects').

A relationship between ovarian cancer risk and low dose local vaginal oestrogen therapy is uncertain.

### Venous thromboembolism

HRT is associated with a 1.3- to 3-fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see Adverse Effects).

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 recognised risk factors for VTE include use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m<sup>2</sup>), pregnancy/postpartum period, systemic lupus erythematosus (SLE) and cancer. There is no consensus about the possible role of varicose veins in VTE.

A relationship between venous thromboembolism and low dose local vaginal oestrogen therapy is uncertain.

As in all postoperative patients, prophylactic measures need to be considered to prevent VTE following surgery. If prolonged immobilisation 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 a young age, screening may be offered after careful counselling 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.

Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

If VTE develops after initiating therapy, the drug 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 randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestagen or oestrogen-only therapy.

#### Ischaemic stroke

Combined oestrogen-progestagen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT increase with age (see Adverse Effects).

A relationship between ischaemic stroke and low dose local vaginal oestrogen therapy is uncertain.

#### Other conditions

Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.

Women with pre-existing hypertriglyceridaemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.

The relationship between pre-existing hypertriglyceridaemia and low dose local vaginal oestrogen therapy is unknown.

Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone (as measured by protein-bound iodine (PBI)), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

HRT does not improve cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65.

Intravaginal applicator may cause minor local trauma, especially in women with serious vaginal atrophy.

### **Use in Pregnancy**

Pregnancy Category: B3

Vagifem and Vagifem Low are contraindicated during pregnancy. If pregnancy occurs during medication with Vagifem or Vagifem Low treatment should be withdrawn immediately. In animal studies, maternal administration of high doses of oestrogens has produced urogenital malformations in the offspring. The relevance of these animal findings for the clinical use of oestradiol is uncertain, but is considered likely to be low.

### **Use in Lactation**

Vagifem and Vagifem Low are not indicated during lactation.

### **Use in the Elderly**

The experience of treating women older than 65 years of age is limited.

## **Adverse Effects**

### **Clinical trial experience**

More than 692 patients have been treated with Vagifem Low in clinical trials, including over 456 patients treated up to 52 weeks. The most commonly reported adverse drug reactions were vulvovaginal mycotic infection and vulvovaginal pruritis. More than 640 patients have been treated with Vagifem 25 micrograms in clinical trials, including over 200 patients treated from 28 weeks and up to 64 weeks. The most commonly reported adverse drug reactions were vaginal discharge and vaginal discomfort.

If noted, oestrogen-related adverse events such as breast pain, peripheral oedema and postmenopausal bleeding were most likely to be present at the beginning of Vagifem or Vagifem Low treatment.

Adverse drug reactions which occurred with a higher frequency in the treated group as compared with the placebo group, and which are possibly related to treatment, are presented below.

Table 2 Adverse drug reactions observed in clinical trials with Vagifem.

<b>System organ class</b>	<b>Common ≥1/100; &lt;1/10</b>	<b>Uncommon ≥1/1,000; &lt;1/100</b>	<b>Rare ≥1/10,000; &lt;1/1,000</b>
<b>Infections and infestations</b>	Genital candidiasis or vaginitis, see also “Reproductive system and breast disorders”		
<b>Nervous system disorders</b>	Headache		
<b>Gastrointestinal disorders</b>	Nausea Abdominal pain, abdominal distension or abdominal discomfort Dyspepsia Vomiting Flatulence		
<b>Reproductive system and breast disorders</b>	Vaginal haemorrhage, vaginal discharge or vaginal discomfort  Breast oedema, breast enlargement, breast pain or breast tenderness		
<b>General disorders and administration site conditions</b>	Oedema peripheral		

Table 3. Adverse drug reactions observed in clinical trials with Vagifem Low

<b>System organ class</b>	<b>Common ≥1/100; &lt;1/10</b>	<b>Uncommon ≥1/1,000; &lt;1/100</b>	<b>Rare ≥1/10,000; &lt;1/1,000</b>
<b>Infections and infestations</b>		Vulvovaginal mycotic infection	
<b>Nervous system disorders</b>	Headache		
<b>Gastrointestinal disorders</b>	Abdominal pain	Nausea	
<b>Reproductive system and breast disorders</b>	Vaginal haemorrhage, vaginal discharge or vaginal discomfort		
<b>Skin and subcutaneous tissue disorders</b>		Rash	
<b>Investigations</b>		Weight increased	
<b>Vascular disorders</b>		Hot flush Hypertension	

Some absorption of oestradiol may occur and therefore systemic effects of oestrogen might be possible.

### **Post-marketing experience**

In addition to the above mentioned adverse drug reactions, those presented below have been spontaneously reported for patients being treated with Vagifem (25 micrograms), and are considered possibly related to treatment. The reporting rate of these spontaneous adverse drug reactions is very rare (<1/10,000 patient years). Post-marketing experience is subject to underreporting especially with regard to trivial and well known adverse drug reactions. The presented frequencies should be interpreted in that light:

- Neoplasms benign and malignant (incl cysts and polyps): Breast cancer, endometrial cancer
- Immune system disorders: Generalized hypersensitivity reactions (e.g. anaphylactic reaction/shock)
- Metabolism and nutrition disorders: Fluid retention
- Psychiatric disorders: Insomnia, depression
- Nervous system disorders: Migraine aggravated
- Vascular disorders: Deep venous thrombosis
- Gastrointestinal disorders: Diarrhoea
- Skin and subcutaneous tissue disorders: Urticaria, rash erythematous, rash NOS (not otherwise specified), rash pruritic, genital pruritus
- Reproductive system and breast disorders: Endometrial hyperplasia, vaginal irritation, vaginal pain, vaginismus, vaginal ulceration
- General disorders and administration site conditions: Drug ineffective
- Investigations: Weight increased, blood oestrogen increased

Other adverse reactions have been reported in association with oestrogen treatment. Risk estimates have been drawn from systemic exposure and it is not known how these apply to local treatments:

- Myocardial infarction, congestive heart disease
- Gall bladder disease
- Stroke
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura, pruritus
- Endometrial cancer (see Warnings and Precautions), endometrial hyperplasia
- Increase in size of uterine fibroids
- Insomnia
- Epilepsy
- Libido disorder
- Deterioration of asthma
- Probable dementia (see Warnings and Precautions)

### **Breast cancer risk**

Risk estimates have been drawn from systemic exposure and it is not known how these apply to local treatments.

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen therapy for more than 5 years.
- Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestagen combinations.
- The level of risk is dependent on the duration of use (see Warnings and Precautions).
- Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

Million Women Study – Estimated additional risk of breast cancer after 5 years' use

<u>Age range (years)</u>	<u>Incidence per 1000 never-users of HRT over a 5 year period*</u>	<u>Risk ratio#</u>	<u>Additional cases per 1000 HRT users over 5 years (95% CI)</u>
<b>Oestrogen only HRT</b>			
50 – 65	9 – 12	1.2	1 - 2 (0 - 3)
<b>Combined oestrogen-progestagen</b>			
50 - 65	9 - 12	1.7	6 (5 - 7)
* Taken from baseline incidence rates in developed countries.			
# Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use.			
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

US WHI studies – additional risk of breast cancer after 5 years' use

<u>Age range (years)</u>	<u>Incidence per 1000 women in placebo arm over 5 years</u>	<u>Risk ratio and 95% CI</u>	<u>Additional cases per 1000 HRT users over 5 years (95% CI)</u>
<b>CEE oestrogen-only</b>			
50 – 79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0) *
<b>CEE+MPA oestrogen &amp; progestagen‡</b>			
50 - 79	17	1.2 (1.0 - 1.5)	+4 (0 - 9)

\* WHI study in women with no uterus, which did not show an increase in risk of breast cancer

‡When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.

Endometrial cancer risk

Postmenopausal women with a uterus

The endometrial cancer risk is about 5 in every 1,000 women with a uterus not using HRT.

In women with a uterus, use of systemic oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see Warnings and Precautions). Depending on the duration of systemic oestrogen-only use and oestrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1,000 women between the ages of 50 and 65. Adding a progestagen to systemic oestrogen-only therapy for at least 10 days per cycle can prevent this increased risk. In the Million Women Study the use of five years' of combined (sequential or continuous) HRT did not increase risk of endometrial cancer (RR of 1.0 (0.8-1.2)). Please also see Warnings and Precautions.

Ovarian cancer

Risk estimates have been drawn from systemic exposure and it is not known how these apply to local treatments. Long-term use of oestrogen-only and combined oestrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer. In the Million Women Study, 5 years' of HRT resulted in 1 extra case per 2500 users.

Risk of venous thromboembolism

Risk estimates have been drawn from systemic exposure and it is not known how these apply to local treatments. HRT is associated with a 1.3-3 fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HRT (see Warnings and Precautions'. Results of the WHI studies are presented:

#### WHI Studies – Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1000 HRT users
<b>Oral oestrogen-only*</b>			
50 - 59	7	1.2 (0.6 - 2.4)	1 (-3 – 10)
<b>Oral combined oestrogen-progestagen</b>			
50 - 59	4	2.3 (1.2 - 4.3)	5 (1 - 13)

\* Study in women with no uterus

#### Risk of coronary artery disease

Risk estimates have been drawn from systemic exposure and it is not known how these apply to local treatments. The risk of coronary artery disease is slightly increased in users of combined oestrogen-progestagen HRT over the age of 60 (see Warnings and Precautions).

#### Risk of ischaemic stroke

Risk estimates have been drawn from systemic exposure and it is not known how these apply to local treatments. The use of oestrogen-only and oestrogen-progestagen therapy is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT. This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age, see Warnings and Precautions.

#### WHI studies combined – Additional risk of stroke\* over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1000 HRT users over 5 years
50 - 59	8	1.3 (1.1 – 1.6)	3 (1 – 5)

\*No differentiation was made between ischaemic and haemorrhagic stroke

## Interactions

Due to the local administration of the low doses of oestradiol in Vagifem and Vagifem Low, interactions of clinical relevance are not expected.

However, the metabolism of oestrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, 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.

## Overdosage

Vagifem and Vagifem Low are intended for intravaginal use only and the dose of oestradiol is low. Treatment should be symptomatic. An overdose of oestrogen may cause nausea and vomiting

## Pharmaceutical Precautions

Store below 25°C.

Store in a dry place protected from light.

Do not refrigerate.

## Medicine Classification

Prescription Medicine

## Package Quantities

Vagifem and Vagifem Low are modified release pessaries containing 25 microgram or 10 microgram oestradiol (as the hemihydrate), respectively. Each Vagifem or Vagifem Low modified release pessary is inset in a single use, disposable polyethylene/polypropylene applicator. The applicators are packed in PVC/aluminium foil blister packs.

Vagifem: 15 pessaries per carton.

15 pack - 3 blister packs each containing 5 applicators with inset modified release pessaries

Vagifem Low: 6, 8, 18 or 24 pessaries per carton

6 pack - 1 blister pack containing 6 applicators with inset modified release pessaries

8 pack - 2 blister packs each containing 4 applicators with inset modified release pessaries

18 pack - 3 blister packs each containing 6 applicators with inset modified release pessaries

24 pack - 4 blister packs each containing 6 applicators with inset modified release pessaries

Not all pack sizes are marketed.

Each Vagifem tablet is contained in a single-use high density polyethylene / polypropylene applicator.

The applicator with inset tablet is packed in a laminated blister pack consisting of aluminium foil and polyvinyl chloride foil.

## Further Information

### List of Excipients

Lactose monohydrate

Maize starch

Magnesium stearate

Hypromellose

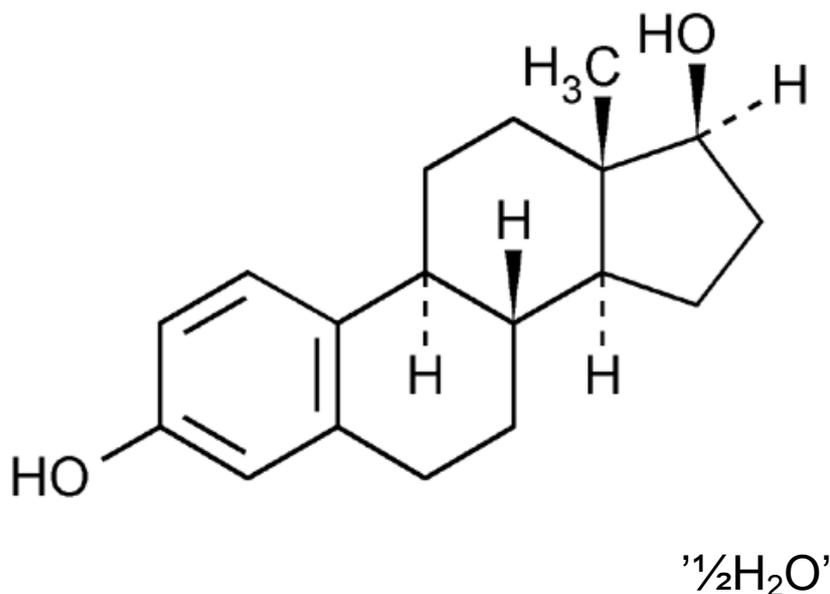
Macrogol 6000

### Active Ingredient

Active ingredients: oestradiol - chemical name: *estra-1,3,5(10)-triene-3,17 $\beta$ -diol* (as hemihydrate). Oestradiol hemihydrate is a white or almost white crystalline powder which is practically insoluble in water and soluble in acetone. Oestradiol hemihydrate has 5 chiral centres. The molecular formula is  $C_{18}H_{24}O_2 \cdot \frac{1}{2} H_2O$ . Oestradiol hemihydrate has a molecular weight of 281.39.

## Structure

Oestradiol hemihydrate



CAS no.: 35380-71-3

### Clinical Trials

Vag-2195 was a 12-month double-blind, randomised, parallel group, placebo-controlled multicenter study was conducted to evaluate the efficacy and safety of Vagifem Low in the treatment of postmenopausal symptoms of vaginal atrophy. Subjects were predominantly Caucasian (92.9%) and had a mean age of 57.6 years, BMI of 25 kg/m<sup>2</sup>, and were on average 8.1 years from last menses. The primary efficacy endpoints were the mean change from baseline to week 12 in: 1) Vaginal Maturation Index (parabasal and superficial cells) and Value; 2) Vaginal pH; and 3) the moderate to severe symptom that was identified by the subject as being most bothersome.

Vaginal Maturation Index (MI) was expressed as percentages of parabasal, intermediate, and superficial cells. The Vaginal Maturation Value (MV) was calculated using:  $MV = 0 \times \% \text{ parabasal cells} + 0.5 \times \% \text{ intermediate cells} + 1.0 \times \% \text{ superficial cells}$ . Vaginal pH was recorded within four intervals (< 5, 5-5.49, 5.5-6.49, and >6.49). These observations were graded on a 4-point scale (no atrophy=0, mild=1, moderate=2, or severe=3 respectively).

After 12 weeks of treatment with Vagifem Low, significant improvements from baseline and versus placebo were demonstrated for the three primary endpoints. Cytologically, a shift towards normalisation in the proportion of parabasal, intermediate, and superficial cells was apparent after Week 2 and sustained through the Week 52 evaluation point ( $p < 0.001$ ).

**Parabasal cells:** The mean change from baseline to Week 12 (LOCF) for Vagifem Low was -37.0% compared to -9.3% for the placebo group ( $p < 0.001$ ).

**Superficial cells:** At baseline, the proportion of superficial cells was < 5%. After 2 weeks of daily administration with Vagifem Low, superficial cells comprised approximately 27% of the total cell count, which was statistically significant compared to placebo treatment ( $p < 0.001$ ). The mean change from baseline to Week 12 (LOCF) was 13.2% compared to 3.8% for placebo ( $p < 0.001$ ).

**Intermediate cells:** The mean change from baseline to Week 12 (LOCF) was approximately 24% ( $p < 0.001$ , compared to placebo).

*Maturation Value (MV)* at Week 12 (LOCF) was 35.9 for placebo and 55.5 for Vagifem Low. The mean change in MV from baseline to Week 12 (LOCF) was 6.5 for placebo and 25.0 for Vagifem Low  $p < 0.001$ . A statistically significant treatment effect was apparent after 2 weeks of study drug administration. The mean change from baseline to Week 2 in MV was 8.3 for placebo and 31.6 for Vagifem Low ( $p < 0.001$ ). These effects were sustained at Week 52 (LOCF): the mean change from baseline for the placebo-treatment group was 5.9 and for Vagifem Low treated subjects was 24.5,  $p < 0.001$ .

*Vaginal pH:* Within 2 weeks of treatment with Vagifem Low, the Vaginal pH Grade was significantly improved versus placebo ( $p < 0.001$ ), which was sustained at the Week 12 (LOCF) ( $p < 0.001$ ) and Week 52 (LOCF) ( $p < 0.001$ ).

Table 2 Vaginal pH - Vagifem Low vs Placebo

Visit	Vaginal pH	Grade	Placebo n (%)	Vagifem Low n (%)
Baseline	< 5	0	0	3 (1.5)
	5-5.49	1	9 (8.8)	26 (12.7)
	5.5-6.49	2	46 (45.1)	90 (44.1)
	> 6.49	3	47 (46.1)	85 (41.7)
Week 12 (LOCF)	< 5	0	7 (6.9)	63 (31.2)
	5 – 5.49	1	30 (29.4)	82 (40.6)
	5.5 – 6.49	2	28 (27.5)	49 (24.3)
	> 6.49	3	37 (36.3)	8 (4.0)
No atrophy = pH < 5, Mild = pH 5-5.49, Moderate = 5.5-6.49, Severe = > 6.49				

*Vaginal health* was assessed based on the examination of vaginal secretions, epithelial integrity, epithelial surface thickness, vaginal colour, and Vaginal pH. These observations were graded on a 4-point scale (no atrophy=0, mild=1, moderate=2, or severe=3). The mean score change at Week 12 (LOCF) was -0.51 and -0.91 for the placebo and Vagifem Low-treated subjects respectively. Treatment benefits were evident after 2 weeks of treatment ( $p < 0.001$ , compared to placebo) and were sustained at Week 52 (placebo -0.36, Vagifem Low -0.84,  $p < 0.001$ ).

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Vagifem is a trade name owned by Novo Nordisk Health Care AG