

## AUSTRALIAN PRODUCT INFORMATION

### VAGIFEM® LOW estradiol 10 µg (as hemihydrate) modified release pessary blister pack

#### 1. NAME OF THE MEDICINE

Estradiol hemihydrate

#### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vagifem Low is an estrogen preparation for intravaginal application based on the active human estrogen estradiol. The Vagifem Low modified release pessary formulation is based on a hydrophilic cellulose-derived matrix which on contact with moisture hydrates and provides a controlled release of estradiol.

Excipient with known effect: lactose monohydrate. For the full list of excipients, see '6.1 List of Excipients.'

#### 3. PHARMACEUTICAL FORM

Estradiol hemihydrate is a white or almost white crystalline powder which is practically insoluble in water and soluble in acetone.

#### 4. CLINICAL PARTICULARS

##### 4.1 Therapeutic Indications

Vagifem Low is indicated for the treatment of atrophic vaginitis due to estrogen deficiency in postmenopausal women.

Vagifem Low is not intended for children or males.

##### 4.2 Dose and Method of Administration

###### Dosage

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

Initial dose: 1 modified release pessary daily for 2 weeks.

Maintenance dose: 1 modified release pessary twice a week.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see '4.4 Special Warnings and Precautions for Use') 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.

###### Method of Administration

Vagifem Low is administered deep intravaginally using the applicator.

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

### 4.3 Contraindications

- Known, suspected or past history of carcinoma of the breast
- Known, suspected or past history of estrogen 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 '4.4 Special Warnings and Precautions for Use')
- 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.

### 4.4 Special Warnings and Precautions for Use

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 therapy with 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 precautions for use. Vaginal infections should be treated before initiation of 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 profile of Vagifem Low shows that there is very low systemic absorption of estradiol during treatment (see '5.2 Pharmacokinetic Properties'), however being an HRT product 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 estrogen treatment. Patients with the following conditions should be monitored frequently and if any of the conditions worsen, Vagifem Low treatment should be withdrawn:

- Leiomyoma (uterine fibroids) or endometriosis
- Liver disorders (e.g. liver adenoma)
- Cholelithiasis
- Risk factors for estrogen 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.

#### 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 '4.8 Adverse Effects (Undesirable 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 '4.3 Contraindications').

Generally recognised risk factors for VTE include use of estrogens, 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 estrogen 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 estrogen-progestagen or estrogen-only therapy.

#### Ischaemic stroke

Combined estrogen-progestagen and estrogen-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 '4.8 Adverse Effects (Undesirable Effects)').

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

#### 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 estrogens should be examined with special care in order to exclude hyperstimulation/malignancy of the endometrium before initiation of treatment with 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 estrogens is dependent on both duration of treatment and on estrogen dose. In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among systemic estrogen-only users varies from 2- to 12-fold compared with non-users, depending on both duration of treatment and on estrogen 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 estrogen 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, estrogen 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 Low.

Unopposed estrogen 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 estrogens 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 estrogen-progestagen and possibly also estrogen-only HRT, that is dependent on the duration of taking HRT.

Observational studies in hysterectomised women using estrogen-only HRT have mostly reported a small increase in risk of having breast cancer diagnosed that is substantially lower than found in users of estrogen-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 estrogen therapy is uncertain.

HRT, especially estrogen-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. Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking estrogen-only or combined estrogen-progestagen HRT, which becomes apparent within 5 years' of use and diminishes over time after stopping. Some other studies, including the WHI trial, suggest that use of combined HRTs may be associated with a similar or slightly smaller risk (see '4.8 Adverse Effects (Undesirable Effects)').

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

### Other conditions

Estrogens 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 estrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition.

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

Estrogens 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 estrogen-only HRT after the age of 65.

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

### Use in elderly

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

### Paediatric use

No data available.

### Effects on laboratory tests

No data available.

## **4.5 Interaction with Other Medicines and Other Form of Interactions**

Due to the local administration of the low dose of estradiol in Vagifem Low, interactions of clinical relevance are not expected.

However, the metabolism of estrogens 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 estrogens.

## 4.6 Fertility, Pregnancy and Lactation

### Effects on fertility

No data available.

### Use in pregnancy

Pregnancy Category: B3

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

### Use in lactation

Vagifem Low is not indicated during lactation.

## 4.7 Effects on Ability to Drive and Use Machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

## 4.8 Adverse Effects (Undesirable 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.

If noted, estrogen-related adverse events such as breast pain, peripheral oedema and postmenopausal bleeding were most likely to be present at the beginning of 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 1.** 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>
<i>Infections and infestations</i>		Vulvovaginal mycotic infection	
<i>Nervous system disorders</i>	Headache		
<i>Gastrointestinal disorders</i>	Abdominal pain	Nausea	
<i>Reproductive system and breast disorders</i>	Vaginal haemorrhage, vaginal discharge or vaginal discomfort		
<i>Skin and subcutaneous tissue disorders</i>		Rash	
<i>Investigations</i>		Weight increased	
<i>Vascular disorders</i>		Hot flush Hypertension	

Some absorption of estradiol may occur and therefore systemic effects of estrogen 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 estradiol 25 microgram vaginal pessary, 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 estrogen 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
- Stroke
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura, pruritus
- Endometrial cancer (see '4.4 Special Warnings and Precautions for Use'), endometrial hyperplasia
- Increase in size of uterine fibroids
- Insomnia
- Epilepsy
- Libido disorder
- Deterioration of asthma
- Probable dementia (see '4.4 Special Warnings and Precautions for Use').

#### *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 estrogen-progestagen therapy for more than 5 years.



- Any increased risk in users of estrogen-only therapy is substantially lower than that seen in users of estrogen-progestagen combinations.
- The level of risk is dependent on the duration of use (see ‘4.4 Special Warnings and Precautions for Use’).
- 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

Age range (years)	Incidence per 1000 never-users of HRT over a 5 year period*	Risk ratio#	Additional cases per 1000 HRT users over 5 years (95% CI)
<b>Estrogen only HRT</b>			
50 – 65	9 – 12	1.2	1 - 2 (0 - 3)
<b>Combined estrogen-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

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 (95% CI)
<b>CEE estrogen-only</b>			
50 – 79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0) *
<b>CEE+MPA estrogen &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 estrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see ‘4.4 Special Warnings and Precautions for Use’). Depending on the duration of systemic estrogen-only use and estrogen 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 estrogen-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 ‘4.4 Special Warnings and Precautions for Use’.

*Ovarian cancer*

Risk estimates have been drawn from systemic exposure and it is not known how these apply to local treatments. Use of estrogen-only or combined estrogen-progestagen HRT has been

associated with a slightly increased risk of having ovarian cancer diagnosed (see ‘4.4 Special Warnings and Precautions for Use’).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2,000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

#### *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 ‘4.4 Special Warnings and Precautions for Use’). 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 estrogen-only*</b>			
50-59	7	1.2 (0.6 - 2.4)	1 (-3 – 10)
<b>Oral combined estrogen-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 estrogen-progestagen HRT over the age of 60 (see ‘4.4 Special Warnings and Precautions for Use’).

#### *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 estrogen-only and estrogen-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 ‘4.4 Special Warnings and Precautions for Use’.

#### 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			

### Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems>.

## **4.9 Overdose**

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## **5. PHARMACOLOGICAL PROPERTIES**

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

### **5.1 Pharmacodynamic Properties**

#### Mechanism of action

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

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

Maturation of the vaginal epithelium is dependent upon estrogen. Estrogen increases the number of superficial and intermediate cells as compared to basal cells.

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

#### 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,  $p < 0.001$ ).

## 5.2 Pharmacokinetic Properties

The modified release pessary formulation of Vagifem Low is based on a hydrophilic cellulose-derived matrix which hydrates on contact with moisture to give a controlled release of the soluble estradiol. 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 estradiol is gradually released from the hydrophilic matrix.

Estrogen drug products are well absorbed through the skin, mucous membranes, and the gastrointestinal tract. The vaginal delivery of estrogens circumvents first-pass metabolism. After treatment with Vagifem Low, marginal elevations of plasma estradiol and its metabolites, have been observed. This indicates that some absorption of estradiol 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 estradiol from Vagifem Low. Subjects were randomised 1:1 to receive either 25 micrograms estradiol (E2) vaginal pessary or 10 micrograms E2 (Vagifem Low). Plasma levels of E2, estrone (E1) and estrone 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 estradiol levels for 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 estradiol levels do not accumulate during twice weekly maintenance therapy (see Table 3).

**Table 3** Values of PK parameters from plasma estradiol (E2) concentrations: Study VAG-1850

	Vagifem Low (10 micrograms E2)	
	$AUC_{(0-24)}$ 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
Day 1	225.35	9.39 [0%]
Day 14	157.47	6.56 [0%]
Day 82	44.95	1.87 [0%]
Day 83	111.41	4.64 [0%]

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

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

### **5.3 Preclinical Safety Data**

#### Genotoxicity

There is limited evidence available in the literature suggesting that estradiol 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 estradiol in human lymphocyte cultures. Importantly, there was no evidence of clastogenicity in rodent bone marrow micronucleus assays.

#### Carcinogenicity

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

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of Excipients**

Pessary core: hypromellose, lactose monohydrate, maize starch, magnesium stearate.  
Film coating: hypromellose, macrogol 6000.

### **6.2 Incompatibilities**

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

### **6.3 Shelf Life**

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

### **6.4 Special Precautions for Storage**

Store below 25°C. Store in a dry place protected from light. Do not refrigerate.

### **6.5 Nature and Contents of Container**

Vagifem Low is a modified release pessary containing 10 micrograms estradiol (as the hemihydrate). Each 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.

Each pessary is white, film-coated, biconvex, 6 mm in diameter, and marked with 'Novo 278' on one side and blank on the other.

- 6 packs - 1 blister pack containing 6 applicators with inset modified release pessaries;
- 8 packs - 2 blister packs each containing 4 applicators with inset modified release pessaries;
- 18 packs - 3 blister packs each containing 6 applicators with inset modified release pessaries;
- 24 packs - 4 blister packs each containing 6 applicators with inset modified release pessaries.

Not all pack sizes may be marketed.

## 6.6 Special Precautions for Disposal

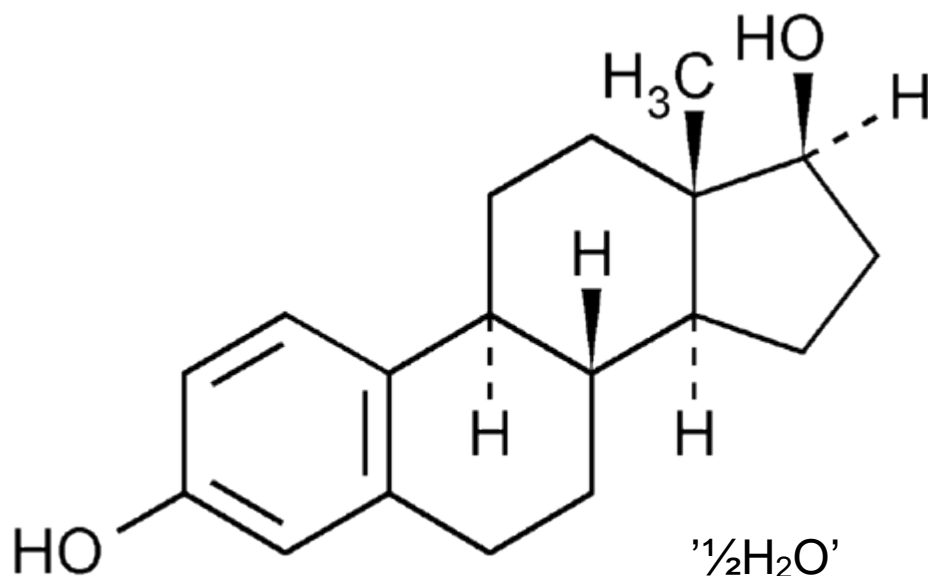
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

## 6.7 Physicochemical Properties

### Chemical structure

Active ingredients: estradiol - chemical name: estra-1,3,5(10)-triene-3,17 $\beta$ -diol (as hemihydrate). Estradiol hemihydrate has 5 chiral centres. The molecular formula is  $C_{18}H_{24}O_2 \cdot \frac{1}{2} H_2O$ .

Estradiol hemihydrate has a molecular weight of 281.39.



### CAS number

CAS no.: 35380-71-3

## 7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 Prescription Only Medicine

## 8. SPONSOR

Novo Nordisk Pharmaceuticals Pty Ltd  
Level 3, 21 Solent Circuit  
Baulkham Hills NSW 2153

## 9. DATE OF FIRST APPROVAL

19 October 2010

## 10. DATE OF REVISION

3 October 2019

**Summary table of changes**

<b>Section changed</b>	<b>Summary of new information</b>
All sections	Updated to new TGA format