

New Zealand Datasheet

Name of Medicine

VAGIFEM[®]

17 β -oestradiol 25 mcg modified release pessary

Presentation

A white, film coated, biconvex modified release pessary marked NOVO 279 on one side, blank on the other side with a diameter of 6mm, and containing 25 mcg of 17 β -oestradiol (as the hemihydrate).

Uses

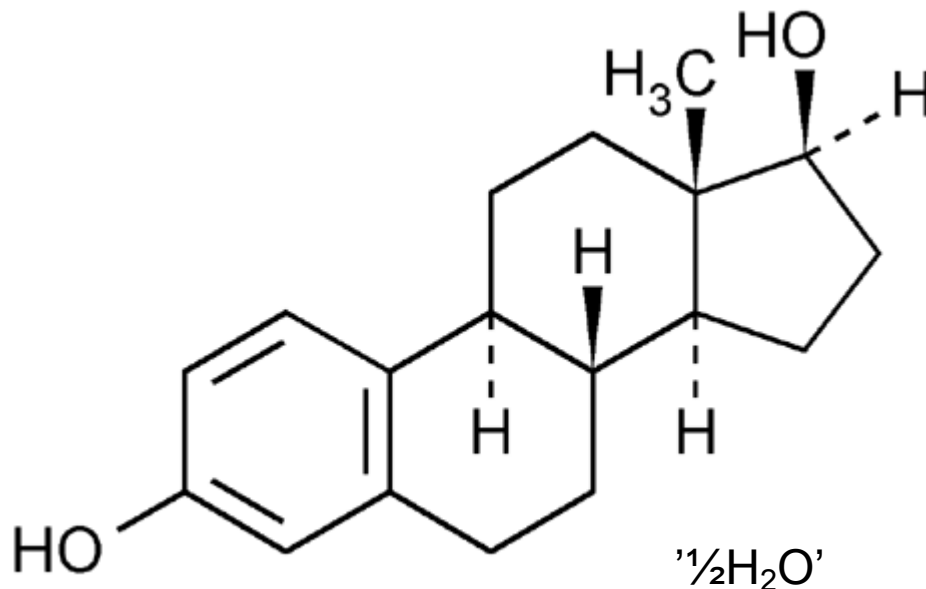
Actions

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

Active ingredients: oestradiol - chemical name: estra-1,3,5(10)-triene-3,17 β -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 C₁₈H₂₄O₂, ½ H₂O. Oestradiol hemihydrate has a molecular weight of 281.39.

Structure

Oestradiol hemihydrate



CAS no.: 35380-71-3

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 relieves the symptoms of atrophic vaginitis due to oestrogen deficiency following the menopause. Vagifem therapy reverses the atrophic changes due to oestrogen deficiency found in the affected post-menopausal vagina.

The active ingredient, synthetic 17β -oestradiol, is chemically and biologically identical to endogenous human oestradiol.

Endogenous 17β -oestradiol induces and maintains the primary and secondary female sexual characteristics. The biological effect of 17β -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 dependent upon oestrogen. Oestrogen increases the number of superficial and intermediate cells as compared to basal cells.

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

Pharmacokinetics

The modified release pessary formulation of Vagifem is 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, marginal elevations of plasma oestradiol and its metabolites as well as 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. Subjects were randomized 1:1 to receive either 25 mcg E2 (Vagifem) or 10 mcg E2. 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 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

	Vagifem 25 µg 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	96.66	4.03
Day 1	476.14	19.84 [54%]
Day 14	438.87	18.29 [37%]
Day 82	48.13	2.01 [0%]
Day 83	225.94	9.41 [15%]

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

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

Indications

Vagifem is indicated for the treatment of atrophic vaginitis due to oestrogen deficiency.

Vagifem is not intended for children or males.

Dosage and Administration

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

Vagifem is administered deeply into the vagina using the applicator.

Initial dose: 1 modified release pessary a day for two 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 should be used (see Warnings and Precautions). Patient review should occur 3-6 months after treatment initiation. Reassessment of risks and benefits should occur no less frequently than annually.

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

Administration

1. Open the blister pack at the plunger end.
2. Insert the applicator in the vagina until resistance is met (8-10 cm).
3. Release the modified release pessary by pressing the plunger.
4. Withdraw the applicator and discard.

Contraindications

- Known hypersensitivity to the active substances or to any of the excipients
- Known or suspected or past history of breast cancer
- Porphyria
- Abnormal genital bleeding of unknown aetiology
- Known or suspected pregnancy
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)
- Known or suspected or past history of oestrogen-dependent neoplasia (e.g. endometrial cancer or other hormone dependent tumour)

- Untreated endometrial hyperplasia
- Acute thrombophlebitis or thromboembolic disorders or a past history of these conditions associated with previous oestrogen use
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal

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.

Medical examination/follow-up

Before initiation of therapy with Vagifem 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 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 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.

Conditions which need supervision

Patients with the following conditions should be monitored frequently and if any of the conditions worsen, Vagifem treatment should be withdrawn:

- Leiomyoma (uterine fibroids) or endometriosis
- Thrombophlebitis, thromboembolic disorders or cerebral vascular accident or a past history of these disorders
- Hypertension requiring treatment
- Acute or chronic liver disease or history of liver disease where liver function tests have failed to return to normal
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus (SLE)
- A history of endometrial hyperplasia
- Epilepsy
- Asthma
- Otosclerosis
- Haemoglobinopathies or sickle-cell anaemia
- Cardiac dysfunction

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

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 cancer

Women with 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 disclose a possible hyperstimulation/malignancy of the endometrium before initiation of treatment with Vagifem.

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. The dose of oestradiol in Vagifem is low and treatment is local. A minor degree of systemic absorption may occur in some patients (see 'Pharmacokinetics'). However, Vagifem has not been associated with an increased risk of endometrial hyperplasia or uterine cancer.

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

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.

Other conditions

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

Use in Pregnancy

Pregnancy Category: B3

Vagifem is not indicated during pregnancy. If pregnancy occurs during medication with Vagifem 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 is 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 640 patients have been treated with Vagifem 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 treatment.

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

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

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

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 µg), 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 (including 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

The following adverse reactions have been reported in association with systemic oestrogen treatment:

- Myocardial infarction, congestive heart disease
- Gall bladder disease
- Stroke
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura, pruritus
- Risk of developing endometrial cancer (see Warnings and Precautions), endometrial hyperplasia or increase in size of uterine fibroids*
- Insomnia
- Epilepsy
- Libido disorder NOS (not otherwise specified)
- Deterioration of asthma
- Probable dementia (see Warnings and Precautions)

* In non-hysterectomised woman

Interactions

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

Overdosage

Vagifem is 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.

Keep out of reach of children.

Medicine Classification

Prescription Medicine

Package Quantities

Vagifem: 15 modified release pessaries per carton.

Each Vagifem modified release pessary is contained in a single-use disposable polyethylene / polypropylene applicator.

The applicator with inset modified release pessary is packed in a laminated blister pack consisting of aluminium foil and PVC.

The blister pack consists of 5 blisters each with an applicator. There are 3 x 5 applicators packed in a carton.

Further Information

Instructions for Use

1. Open the blister pack at the plunger end.
2. Insert the applicator in the vagina until resistance is met (8-10 cm).
3. Release the modified release pessary by pressing the plunger.
4. Withdraw the applicator and discard.

List of Excipients

Lactose monohydrate
Maize starch
Magnesium stearate
Hypromellose
Macrogol 6000

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Name and Address

Novo Nordisk Pharmaceuticals Ltd.
PO Box 51-268
Pakuranga
Auckland

Tel: (09) 916 5590

Fax: (09) 916 5595

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Vagifem is a trade name owned by Novo Nordisk FemCare AG