Professional information for Vagifem® 10 µg

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

Vagifem® 10 µg vaginal tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated vaginal tablet contains:

Estradiol hemihydrate equivalent to estradiol 10 micrograms.

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM

Vaginal tablets.

A white, film-coated, biconvex tablet, engraved with NOVO 278. Diameter 6 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vagifem® 10 µg is indicated for the treatment of atrophic vaginitis due to oestrogen deficiency.

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

4.2 Posology and method of administration

Vagifem® 10 µg is administered intravaginally using the applicator.

Initial dose: One vaginal tablet daily for two weeks.

Maintenance dose: One vaginal tablet twice a week.

Treatment may be started on any convenient day.

If a dose is forgotten, it should be used 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 should be used.

Vagifem® 10 µg may be used in women with or without an intact uterus.

During treatment, especially during the first 2 weeks, absorption may be seen but as plasma estradiol levels usually do not exceed normal postmenopausal levels the addition of a progestagen is not recommended.

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 tablet by pressing the plunger.

4. Withdraw the applicator and discard. The used applicator may be disposed together with household waste.

4.3 Contraindications

- Known history (personal and/or family) 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 vein thrombosis (DVT), pulmonary embolism);
- Inherited thrombophilia or known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency);
- Active or recent arterial thromboembolic disease (e.g. coronary artery disease, angina pectoris, myocardial infarction, stroke);
- Active liver disease. Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal;
- Known hypersensitivity to the active substances or to any of the excipients of Vagifem® (see section 6.1);
- Porphyria;
- Patients known with inherited genetic mutations: BRCA1 and BRCA2 genes;
- Early menstrual periods (before the age of 12 years);
- History of non-cancerous breast diseases (atypical hyperplasia or lobular carcinoma *in situ*);
- Previous treatment using radiation therapy to the chest or breast;
- Previous exposure to diethylstilbestrol (DES).
- Not for use during pregnancy.

4.4 Special warnings and precautions for use

A careful assessment of the risks and benefits should be undertaken at least annually and Vagifem® 10 µg should only be continued as long as there are no contraindications to treatment after 5 years of usage and the benefit outweighs the risk.

Medical examination/follow-up

Before initiating or reinstituting Vagifem® 10 µg therapy, a complete personal and family medical history should be obtained. Physical examination (including pelvic and breast) should be guided by this and by the contraindications and warnings for use.

During treatment, periodic check-ups are recommended at a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse.

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, in particular:

- Leiomyoma (uterine fibroids) or endometriosis;
- A history of, or risk factors for, thromboembolic disorders (see '*Venous thromboembolism'* below);
- 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 '*Endometrial hyperplasia'* 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

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 and during treatment with Vagifem® 10 µg.

In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when systemic oestrogens are administered alone for prolonged periods.

After stopping treatment such risk may remain elevated for at least 10 years.

The risk of endometrial cancer after treatment with oral unopposed oestrogens is dependent on both the duration of treatment and on the oestrogen dose. Systemic absorption may occur in some patients. Because there is no systemic effect under the local oestrogen treatment with Vagifem® 10 µg, the addition of a progestagen is not recommended.

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 should 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® 10 µg.

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

Break-through bleeding and spotting may occur during the first months of treatment with Vagifem® 10 µg. If break-through bleeding or spotting appears after some time on therapy, or continues

after treatment has been discontinued, the reason for the bleeding should be investigated.

The woman should be advised to contact her doctor in case bleeding or spotting occurs during treatment with Vagifem® 10 µg.

Breast cancer

Hormone replacement therapy (HRT) contains oestrogen which, on prolonged use, may increase the risk of developing breast cancer. A meta-analysis of prospective epidemiological studies from 1992 to 2018 reported a significant increase in the risk of developing breast cancer in 55 575 women 40 – 59 years of age who used menopausal hormone therapy (MHT). The risk increased steadily with duration of use and was slightly greater for oestrogen-progestagen than oestrogen only preparations, and the risk persisted for more than 10 years after stopping the treatment. The relative risk (RR) to develop breast cancer for oestrogen-progestagen preparations was 1,60 at 1 – 4 years and RR = 2,08 at 5 – 14 years, while that for oestrogen only preparations were 1,17 at 1 – 4 years and 1,33 at 5 – 14 years. There was no risk to develop breast cancer in women who started MHT at 60 years of age. However, evidence from a meta-analysis study suggested no increase in risk of breast cancer in women with no history of breast cancer taking low dose vaginally applied oestrogens.

All women on Vagifem® 10 µg should receive yearly breast examinations by a health care provider and perform monthly breast self-examinations. Mammography evaluations should be done based on patient age, risk factors, and prior mammogram results.

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

Ovarian cancer

Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined oestrogen-progestagen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping (see section 4.8).

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

Venous thromboembolism

Patients with known thrombophilic states have an increased risk of VTE (venous thromboembolism) and HRT may add to this risk. Vagifem® 10 µg is therefore contraindicated in these patients (see section 4.3).

Generally recognised risk factors for VTE include, use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m^2), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE. 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, such as antithrombin, protein S, or protein C deficiencies or a combination of defects, Vagifem ®10 µg use is contraindicated.

Women already on chronic anticoagulant treatment require careful consideration of benefit-risk of use of Vagifem ®10 µg.

If VTE develops after initiating therapy, Vagifem ®10 µg 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 leg, sudden pain in the chest, dyspnoea).

Systemic HRT is associated with a 1,3 – 3 fold risk of developing 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 section 4.8).

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 increase in risk of ischaemic stroke.

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

Cognitive function

Vagifem® 10 µg use does not improve cognitive function. There is evidence of an increased

risk of dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65.

Other conditions

Women with pre-existing hypertriglyceridaemia should be followed closely during oestrogen replacement or hormone replacement therapy (including Vagifem® 10 µg), since large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition. The relationship between pre-existing hypertriglyceridaemia and Vagifem® 10 µg therapy is unknown.

Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone. 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).

The minimal systemic absorption of estradiol with local vaginal administration (see section 5.2) is likely to result in less pronounced effects on plasma binding proteins than with systemic hormones.

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

Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits

and risks for these women may be more favourable than in older women.

Oestrogens, including Vagifem® 10 µg, may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed during the first weeks of treatment.

4.5 Interaction with other medicines and other forms of interaction

Due to a local administration of Vagifem® 10 µg, interactions of clinical relevance are not expected. However, interactions with other locally applied vaginal treatments should be considered.

The metabolism of oestrogens may be increased by concomitant use of substances known to induce medicine-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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Vagifem® 10 µg is contraindicated during pregnancy. If pregnancy occurs during medication with Vagifem® 10 µg, treatment should be withdrawn immediately.

Lactation

Vagifem® 10 µg is contraindicated during lactation.

4.7 Effects on ability to drive and use machines

No effects known.

4.8 Undesirable effects

The most commonly reported adverse reactions are: vulvovaginal mycotic infection and vulvovaginal pruritus. Oestrogen–related adverse events such as breast pain, peripheral oedema and postmenopausal bleedings have been reported. Those adverse events observed with a higher frequency in patients treated with Vagifem® 10 µg as compared to placebo and which are possibly related to treatment are presented below.

System Organ Class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1 000 to < 1/100)**	**Rare (≥ 1/10 000 to < 1/1 000)**
Infections and infestations:	Genital candidiasis or vaginitis, see also '*Reproductive system and breast disorders*'	Vulvovaginal mycotic infection	
Nervous system disorders:	Headache		
Vascular disorders:		Hot flush, hypertension	
Gastrointestinal	Nausea,		

disorders:	abdominal pain, abdominal distension or abdominal discomfort, dyspepsia, vomiting, flatulence		
Skin and subcutaneous issue disorders:		Rash	
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:	Peripheral oedema		
Investigations:		Increased body mass	

Post-marketing experience:

In addition to the above mentioned adverse reactions, those presented below have been spontaneously reported for patients being treated with Vagifem®, and are considered possibly

related to treatment. The reporting rate of these spontaneous adverse reactions is very rare.

- *Neoplasms benign and malignant (including cysts and polyps):* Breast cancer, endometrial cancer;
- *Immune system disorders:* Generalised 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), pruritic rash, genital pruritus;
- *Reproductive system and breast disorders:* Endometrial hyperplasia, vaginal irritation, vaginal pain, vaginismus, vaginal ulceration;
- *Investigations:* Increased BMI, increased blood oestrogen.

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

- Myocardial infarction, congestive heart disease;
- Stroke;
- Gall bladder disease;
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura, pruritus;
- Risk of developing endometrial cancer, endometrial hyperplasia or increase in size of uterine fibroids;
- Insomnia;
- Epilepsy;

- Libido disorder NOS (not otherwise specified);
- Deterioration of asthma;
- Probable dementia.

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 section 4.3).

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 12 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)).

Ovarian cancer

Use of systemic HRT has been associated with an increased risk of having ovarian cancer diagnosed (see section 4.4).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using systemic 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 who have been taking HRT for 5 years, this results in about 1 extra case per 2 000 users. In women aged 50 to 54 who do not take HRT, about 2 women in 2 000 will be diagnosed with ovarian cancer over a 5-year period.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of Vagifem® 10 µg is important. It allows continued monitoring of the benefit/risk balance of Vagifem® 10 µg. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Vagifem® 10 µg is intended for intravaginal use and the dose of estradiol is very low. Overdose is therefore unlikely, but if it occurs, treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

Category and class: A.21.8.1 Oestrogens

Pharmacotherapeutic group: Natural and semisynthetic oestrogens, plain.

ATC code: G03CA03

The active ingredient, synthetic 17β-estradiol, is chemically and biologically identical to endogenous human estradiol. Endogenous 17β-estradiol induces and maintains the primary and secondary female sexual characteristics. The biological effect of 17β-estradiol is carried out through a number of specific oestrogen receptors. The steroid receptor complex is bound to the DNA cells 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 pH in the vagina down to around 4,5 which enhances normal bacterial flora, e.g. *Lactobacillus Döderlein* predomination.

5.2 Pharmacokinetic properties:

There is no cumulative effect during twice weekly maintenance therapy (see Table 1).

Table 1: Values of PK parameters from plasma estradiol (E2) concentrations

Day	$AUC_{(0-24)}$ pg.h/mL (geom. mean)	$C_{ave\ (0-24)}$ pg/mL (geom. mean)
Day -1 before treatment	75,65	3,15
Day 1	225,35	9,39
Day 14	157,47	6,56
Day 82	44,95	1,87
Day 83	111,41	4,64

The levels of estrone and estrone sulfate seen after 12 weeks of Vagifem® 10 µg administration did not exceed baseline levels.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose (464)

lactose monohydrate

maize starch

magnesium stearate (E572)

macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

Store at or below 25 °C.

6.4 Special precautions for storage

Do not refrigerate.

Keep the blisters in the outer carton until required for use.

6.5 Nature and contents of container

Each film-coated vaginal tablet is contained in a disposable single-use polyethylene/polypropylene applicator.

The applicators are packed in transparent PVC/aluminium foil blisters.

8 packs outer carton contain 2 blister cards of 4 applicators with inset tablets.

18 packs outer carton contain 3 blister cards of 6 applicators with inset tablets.

24 packs outer carton contain 4 blister cards of 6 applicators with inset tablets.

6.6 Special precautions for disposal and other handling

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novo Nordisk (Pty) Ltd

150 Rivonia Road

10 Marion Street Office Park

Building C1

Sandton

Johannesburg 2196

8. REGISTRATION NUMBER

47/21.8.1/0166

9. DATE OF FIRST AUTHORISATION

06 August 2015

10. DATE OF REVISION OF THE TEXT

17 August 2022