SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vagifem 10 micrograms vaginal tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vaginal tablet contains: estradiol hemihydrate equivalent to estradiol 10 micrograms.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Vaginal tablet.

White, film-coated, biconvex tablet, engraved with NOVO 278 on one side. Diameter 6 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of vaginal atrophy due to oestrogen deficiency in postmenopausal women (see section 5.1).

The experience treating women older than 65 years is limited.

4.2 Posology and method of administration

Vagifem is administered intravaginally as a local oestrogen therapy by use of an 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 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 also section 4.4) should be used.

For oestrogen products for vaginal application of which the systemic exposure to the oestrogen remains within the normal postmenopausal range, such as Vagifem, it is not recommended to add a progestagen (but see section 4.4, 'Special warnings and precautions for use', 'Endometrial hyperplasia and carcinoma').

Vagifem may be used in women with or without an intact uterus.
Vaginal infections should be treated before start of the Vagifem therapy.

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.

4.3 Contraindications

- Known, past or suspected breast cancer
- Known, past or suspected oestrogen-dependent malignant tumours (e.g endometrial cancer)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4)
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal
- Known hypersensitivity to the active substances or to any of the excipients
- Porphyria.

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually, and HRT should only be continued as long as the benefit outweighs the risk.

Medical examination/follow-up

Before initiating or reinstituting hormone therapy, a complete personal and family medical history should be obtained. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their

breasts should be reported to their doctor or nurse (see 'Breast cancer' below). Investigations including appropriate imaging tools, e.g. mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

The pharmacokinetic profile of Vagifem shows that there is very low systemic absorption of estradiol during treatment (see section 5.2), however, being an HRT product the following need to be considered, especially for long-term or repeated use of this product.

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
- Risk factors for thromboembolic disorders (see below)
- Risk factors for oestrogen-dependent tumours, e.g. 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis.

The pharmacokinetic profile of Vagifem shows that there is very low absorption of estradiol during treatment (see section 5.2). Due to this, the recurrence or aggravation of the above mentioned conditions is less likely than with systemic oestrogen treatment.

Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contraindication is discovered and in the following situations:

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

Endometrial hyperplasia and carcinoma

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.

In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when systemic oestrogens are administered alone for prolonged periods. For oestrogen products for vaginal application of which the systemic exposure to oestrogen remains within the normal postmenopausal range, such as Vagifem, it is not recommended to add a progestagen.

During Vagifem treatment, a minor degree of systemic absorption may occur in some patients, especially during the first two weeks of once-daily administration. However, average plasma E2 concentrations ($C_{ave\ (0\text{-}24)}$) at all evaluated days remained within the normal postmenopausal range in all subjects (see section 5.2).

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.

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.

*The following risks have been associated with **systemic** HRT and apply to a lesser extent for oestrogen products for vaginal application of which the systemic exposure to the oestrogen remains **within** the normal postmenopausal range. However, they should be considered in case of long term or repeated use of this product.*

Breast cancer

Epidemiological evidence from a large meta-analysis suggests no increase in risk of breast cancer in women with no history of breast cancer taking low dose vaginally applied oestrogens. It is unknown if low dose vaginal oestrogens stimulate recurrence 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 oestrogen-only **systemic** HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.

Venous thromboembolism

Systemic 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 section 4.8).

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

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.

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)

Randomised controlled data found no increased risk of CAD in hysterectomised women using **systemic** oestrogen-only therapy.

Ischaemic stroke

Systemic oestrogen-only therapy is 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 increases with age (see section 4.8).

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.

Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

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 radioimmunoassay) or T3 levels (by radioimmunoassay). 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).

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

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the vaginal administration and minimal systemic absorption, it is unlikely that any clinically relevant drug interactions will occur with Vagifem. However, interactions with other locally applied vaginal treatments should be considered.

4.6 Fertility, pregnancy and lactation

Vagifem is not indicated during pregnancy. If pregnancy occurs during medication with Vagifem, treatment should be withdrawn immediately. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to oestrogens indicate no teratogenic or foetotoxic effects.

Lactation

Vagifem is not indicated during lactation.

4.7 Effects on ability to drive and use machines

No effects known.

4.8 Undesirable effects

Adverse events from clinical trials:

More than 673 patients have been treated with Vagifem 10 micrograms in clinical trials, including over 497 patients treated up to 52 weeks.

Oestrogen-related adverse events such as breast pain, peripheral oedema and postmenopausal bleedings have been reported with Vagifem 10 micrograms at very low rates, similar to placebo, but if they occur, they are most likely present only at the beginning of the treatment. The adverse events observed with a higher frequency in patients treated with Vagifem 10 micrograms 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		Vulvovaginal mycotic infection	
Nervous system disorders	Headache		
Gastrointestinal disorders	Abdominal pain	Nausea	
Reproductive system and breast disorders	Vaginal haemorrhage, vaginal discharge or vaginal		

System organ class	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000
	discomfort		
Skin and subcutaneous tissue disorders		Rash	
Investigations		Weight increased	
Vascular disorders		Hot flush Hypertension	

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 10 micrograms and are considered possibly related to treatment. The frequencies for the below mentioned adverse drug reactions cannot be interpreted because these reactions are reported voluntarily from a population of uncertain size:

- 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
- Nervous system disorders: migraine aggravated
- Vascular disorders: deep vein thrombosis
- Gastrointestinal disorders: diarrhoea
- Skin and subcutaneous tissue disorders: pruritus, rash, urticaria
- Reproductive system and breast disorders: endometrial hyperplasia, vulvovaginal pain[1], pruritus genital
- General disorders and administration site conditions: application site reaction[2], drug ineffective, injury associated with device[3]

[1] Including Vulvovaginal burning sensation
[2] Local allergic reactions including Vulvovaginal erythema, Genital erythema, Vulvovaginal rash, Genital rash
[3] Minor local trauma caused by intravaginal applicator

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

- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia over the age of 65 (see section 4.4).

Class effects associated with systemic HRT

The following risks have been associated with systemic HRT and apply to a lesser extent for oestrogen products for vaginal application of which the systemic exposure to oestrogen remains within the normal postmenopausal range.

Ovarian cancer

Use of **systemic** HRT has been associated with a slightly 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 2000 will be diagnosed with ovarian cancer over a 5-year period.

Risk of venous thromboembolism

Systemic HRT is associated with a 1.3- to 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 section 4.4). Results of the WHI studies are presented below:

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

Age range (years)	Incidence per 1,000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1,000 HRT users
Oral oestrogen-only*			
50 – 59	7	1.2 (0.6 – 2.4)	1 (-3 – 10)

* Study in women with no uterus.

Risk of ischaemic stroke

The use of **systemic** HRT is associated with an up to 1.5-fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during the 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 section 4.4).

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

Age range (years)	Incidence per 1,000 women in	Risk ratio and 95% CI	Additional cases per 1,000 HRT

	placebo arm over 5 years		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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 cells' DNA and induces synthesis of specific proteins.

Maturation of the vaginal epithelium is dependent upon oestrogens. Oestrogens increase the number of superficial and intermediate cells and decrease the number of basal cells in vaginal smear.

Oestrogens maintain vaginal pH around normal range (4.5) which enhances normal bacterial flora.

Treatment of vaginal oestrogen deficiency symptoms: vaginally applied oestrogen alleviates the symptoms of vaginal atrophy due to oestrogen deficiency in postmenopausal women.

A 12-months, double-blind, randomised, parallel group, placebo-controlled, multicentre study was conducted to evaluate the efficacy and safety of Vagifem 10 micrograms in the treatment of postmenopausal vaginal atrophy symptoms.

After 12 weeks of treatment with Vagifem 10 micrograms, the change from baseline, in comparison with placebo treatment, demonstrated significant improvements in the three primary endpoints: Vaginal Maturation Index and Value, normalisation of vaginal pH and relief of the moderate/severe urogenital symptoms considered most bothersome by the subjects.

Endometrial safety of Vagifem 10 micrograms was evaluated in the above mentioned trial and a second, open-label, multicentre trial. In total, 386 women underwent endometrial biopsy at the beginning and at the end of 52 weeks treatment. Incidence rate of hyperplasia and/or carcinoma was 0.52% (95% CI 0.06%, 1.86%), indicating no increased risk.

5.2 Pharmacokinetic properties

Absorption

Oestrogens are well absorbed through the skin, mucous membranes and the gastrointestinal tract. After vaginal administration, estradiol is absorbed circumventing first-pass metabolism.

A 12-weeks, single-centre, randomised, open-label, multiple dose, parallel-group trial was conducted to evaluate the extent of systemic absorption of estradiol from the Vagifem 10 micrograms tablet. Subjects were randomised 1:1 to receive either 10 micrograms or 25 micrograms Vagifem. Plasma levels of estradiol (E2), oestrone (E1) and oestrone sulfate (E1S) were determined. The AUC(0-24) for plasma E2 levels increased almost proportionally after the administration of 10 micrograms and 25 micrograms Vagifem. The AUC(0-24) indicated higher systemic estradiol levels for the 10 micrograms E2 tablet as compared to baseline on treatment days 1, 14 and 83, being statistically significant at days 1 and 14 (Table 1). However, average plasma E2 concentrations (Cave (0-24)) at all evaluated days remained within the normal postmenopausal range in all subjects. The data from days 82 and 83 as compared to baseline indicate that there is no cumulative effect during twice-weekly maintenance therapy.

Table 1 Values of PK parameters from plasma Estradiol (E2) concentrations: Vagifem 10 micrograms

	AUC(0-24) pg.h/ml (geom. mean)	Cave (0-24) pg/ml (geom. mean)
Day -1	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 oestrone and oestrone sulfate seen after 12 weeks of Vagifem 10 micrograms administration did not exceed baseline levels, i.e. no accumulation of oestrone or oestrone sulfate was observed.

Distribution

The distribution of exogenous oestrogens is similar to that of endogenous oestrogens. Oestrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Oestrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Biotransformation

Exogenous oestrogens are metabolized in the same manner as endogenous oestrogens. The metabolic transformations take place mainly in the liver. Estradiol is converted reversibly to oestrone and both can be converted to estriol which is the major urinary metabolite. In postmenopausal women, a significant portion of the circulating oestrogens exists as sulfate conjugates, especially oestrone sulfate, which serves as a circulating reservoir for the formation of more active oestrogens.

Elimination

Estradiol, oestrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

Special patient groups

The extent of systemic absorption of estradiol during treatment with Vagifem 10 micrograms has been evaluated in postmenopausal women aged 60–70 (mean age 65.4) only.

5.3 Preclinical safety data

17β-estradiol is a well-known substance. Non-clinical studies provided no additional data of relevance to clinical safety beyond those already included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Hypromellose

Lactose monohydrate

Maize starch

Magnesium stearate

Film-coating:

Hypromellose

Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not refrigerate.

6.5 Nature and contents of container

Each tablet is contained in a disposable single-use polyethylene/polypropylene applicator. The applicators are packed separately in PVC/aluminium foil blisters.

18 vaginal tablets with applicators.

24 vaginal tablets with applicators.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

17β-estradiol is expected to pose a risk to the aquatic environment, especially to fish populations.

7 MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S

Novo Allé

DK-2880 Bagsværd

Denmark

8 MARKETING AUTHORISATION NUMBER(S)

PL 04668/0237

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/02/2010

10 DATE OF REVISION OF THE TEXT

17/04/2025