SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

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.

Vagifem is a local vaginal therapy and in women with an intact uterus, progestagen treatment is not necessary (however 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. 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 a 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

Vagifem is a locally acting low dose estradiol preparation and therefore the occurrence of the below mentioned conditions is less likely than with systemic oestrogen treatment.

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 oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among systemic oestrogen-only users varies from 2- to 12-fold compared with non-users, depending on both duration of treatment and on oestrogen dose. After stopping treatment, risk may remain elevated for at least 10 years.

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.

Breast cancer

The overall evidence suggests an increased risk of breast cancer in women taking combined oestrogen-progestagen and possibly also oestrogen-only HRT, that is dependent on the duration of taking HRT.

The WHI trial found no increase in risk of breast cancer in hysterectomised women using oestrogen-only HRT. Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is substantially lower than found in users of oestrogen-progestagen combinations.

The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment.

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

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

Ovarian cancer

Ovarian cancer is much rarer than breast cancer. Long-term (at least 5-10 years) use of oestrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer. Some studies including the WHI trial suggest that the long-term use of combined HRT may confer a similar or slightly smaller risk (see section 4.8).

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

Venous thromboembolism

HRT is associated with a 1.3- to 3-fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see 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/m²), pregnancy/postpartum period, systemic lupus erythematosus (SLE) and cancer. There is no consensus about the possible role of varicose veins in VTE.

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

As in all postoperative patients, prophylactic measures need to be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery, temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.

In women with no personal history of VTE but with a first degree relative with a history of thrombosis at a young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening).

If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is ‘severe’ (e.g. antithrombin, protein S, or protein C deficiencies or a combination of defects)

HRT is contraindicated.

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

If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD)

There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestagen or oestrogen-only therapy.

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

Ischaemic stroke

Combined oestrogen-progestagen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT increase with age (see section 4.8).

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

Other conditions

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

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

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

Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone (as measured by protein-bound iodine (PBI)), T4 levels (by column or by 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

As the oestrogen in Vagifem is administered within the vagina and due to the low levels of estradiol released, it is unlikely that any clinically relevant drug interactions will occur with Vagifem.

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

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St John's Wort (*Hypericum perforatum*) may induce the metabolism of oestrogens.

4.6 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 at very low rates, similar to placebo, with Vagifem 10 micrograms, 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	

System organ class	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000
Nervous system disorders	Headache		
Gastrointestinal disorders	Abdominal pain	Nausea	
Reproductive system and breast disorders	Vaginal haemorrhage, vaginal discharge or vaginal 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 25 micrograms, and are considered possibly related to treatment. The reporting rate of these spontaneous adverse reactions is very rare (<1/10,000 patient years).

- 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
- Nervous system disorders: migraine aggravated
- Vascular disorders: deep venous thrombosis
- Gastrointestinal disorders: diarrhoea
- Skin and subcutaneous tissue disorders: urticaria, rash erythematous, rash pruritic, genital pruritus
- Reproductive system and breast disorders: endometrial hyperplasia, vaginal irritation, vaginal pain, vaginismus, vaginal ulceration
- General disorders and administration site conditions: drug ineffective
- Investigations: weight increased, blood oestrogen increased.

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

- Myocardial infarction, congestive heart disease
- Stroke
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Increase in size of fibroids

- Epilepsy
- Libido disorder
- Deterioration of asthma
- Probable dementia over the age of 65 (see section 4.4).

Breast cancer risk

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

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen therapy for more than 5 years.
- Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestagen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- 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 1,000 never-users of HRT over a 5 year period*	Risk ratio and 95% CI #	Additional cases per 1,000 HRT users over 5 years (95% CI)
		Oestrogen only HRT	
50 – 65	9 – 12	1.2	1 – 2 (0 – 3)
		Combined oestrogen-progestagen	
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 1,000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1,000 HRT users over 5 years (95% CI)
		CEE oestrogen-only	
50 – 79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*
		CEE+MPA oestrogen & progestagen‡	
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 1000 women with an 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 4.4).
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 1000 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)).
Please also see section 4.4.

Ovarian cancer

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

Long-term use of oestrogen-only and combined oestrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer. In the Million Women Study, 5 years of HRT resulted in 1 extra case per 2,500 users.

Risk of venous thromboembolism

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

HRT is associated with a 1.3- 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:

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)
Oral combined oestrogen-progestagen			
50 – 59	4	2.3 (1.2 – 4.3)	5 (1 – 13)

* Study in women with no uterus.

Risk of coronary artery disease

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

The risk of coronary artery disease is slightly increased in users of combined oestrogen-progestagen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke

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

The use of oestrogen-only and oestrogen-progestagen therapy is associated with an up to 1.5-fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.

This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age, see section 4.4.

WHI studies combined – Additional risk of ischaemic stroke* 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 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 national reporting system listed in Appendix V.

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.

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 ($C_{ave\ (0-24)}$) 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)	$C_{ave\ (0-24)}$ 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 exist 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 SPC.

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)

<To be completed nationally>

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<To be completed nationally>

10 DATE OF REVISION OF THE TEXT

<To be completed nationally>

<Detailed information on this medicinal product is available on the website of: {name of MS/Agency}>

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Vagifem 10 micrograms vaginal tablets
Estradiol

2. STATEMENT OF ACTIVE SUBSTANCE

Each vaginal tablet contains:
Estradiol 10 micrograms (as estradiol hemihydrate)

3. LIST OF EXCIPIENTS

hypromellose, lactose, maize starch, magnesium stearate and macrogol 6000

4. PHARMACEUTICAL FORM AND CONTENTS

18 vaginal tablets with applicators
24 vaginal tablets with applicators

5. METHOD AND ROUTE OF ADMINISTRATION

For vaginal use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

<To be completed nationally>

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBERS

<To be completed nationally>

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

<To be completed nationally>

15. INSTRUCTIONS ON USE

<To be completed nationally>

16. INFORMATION IN BRAILLE

Vagifem 10 micrograms

<To be completed nationally>

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Vagifem 10 micrograms vaginal tablets
Estradiol
For vaginal use

2. NAME OF MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. OTHER

PACKAGE LEAFLET

Package leaflet: Information for the user

Vagifem 10 micrograms vaginal tablets

Estradiol

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vagifem is and what it is used for

Vagifem contains estradiol
- Estradiol is a female sex hormone.
- It belongs to a group of hormones called oestrogens.
- It is exactly the same as the estradiol produced by the ovaries of women.

Vagifem belongs to a group of medicines called local Hormone Replacement Therapy (HRT).

It is used to relieve menopausal symptoms in the vagina such as dryness or irritation. In medical terms this is known as 'vaginal atrophy'. It is caused by a drop in the levels of oestrogen in your body. This happens naturally after the menopause.

Vagifem works by replacing the oestrogen which is normally produced in the ovaries of women. It is inserted into your vagina, so the hormone is released where it is needed. This may relieve discomfort in the vagina.

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

2. What you need to know before you use Vagifem

Medical history and regular check-ups

The use of HRT carries risks which need to be considered when deciding whether to start taking it, or whether to carry on taking it.

Before you start (or restart) HRT, your doctor will ask about your own and your family's medical history. Your doctor may decide to perform a physical examination. This may include an examination of your breasts and/or internal examination, if necessary.

Go for regular breast screening as recommended by your doctor.

Do not use Vagifem:
If any of the following applies to you. If you are not sure about any of the points below, **talk to your doctor** before using Vagifem.

Do not use Vagifem if
- You are **allergic** (hypersensitive) to **estradiol** or any of the other ingredients of Vagifem (listed in section 6 'Contents of the pack and other information').
- You have or have ever had **breast cancer,** or you are suspected of having it.
- You have or have ever had **cancer which is sensitive to oestrogens,** such as cancer of the womb lining (endometrium), or you are suspected of having it.
- You have **any unexplained vaginal bleeding.**
- You have excessive **thickening of the womb lining** (endometrial hyperplasia) that is not being treated.
- You have or have ever had a **blood clot in a vein** (thrombosis), such as in the legs (deep venous thrombosis) or the lungs (pulmonary embolism).
- You have a **blood clotting disorder** (such as protein C, protein S or antithrombin deficiency).
- You have or have recently had a disease caused by blood clots in the arteries, such as a **heart attack, stroke** or **angina.**
- You have or have ever had a **liver disease** and your liver function tests have not returned to normal.
- You have a rare blood problem called **'porphyria',** which is passed down in families (inherited).

If any of the above conditions appear for the first time while using Vagifem, stop using it at once and consult your doctor immediately.

Warnings and precautions
Tell your doctor if you have or have ever had any of the following problems before you start the treatment. If so, you should see your doctor more often for check-ups. Vagifem, as opposed to systemic oestrogen, is for local treatment in the vagina, and the absorption into the blood is very low. It is therefore less likely that the conditions mentioned below will get worse or come back during treatment with Vagifem.
- Asthma
- Epilepsy
- Diabetes
- Gallstones
- High blood pressure
- Migraines or severe headaches
- A liver disorder, such as a benign liver tumour
- Growth of womb lining outside your womb (endometriosis) or a history of excessive growth of the womb lining (endometrial hyperplasia)
- A disease affecting the eardrum and hearing (otosclerosis)
- A disease of the immune system that affects many organs of the body (systemic lupus erythematosus, SLE)
- Increased risk of getting an oestrogen-sensitive cancer (such as having a mother, sister or grandmother who has had breast cancer)
- Increased risk of developing blood clots (see 'Blood clots in a vein (thrombosis)')
- Fibroids inside your womb
- A very high level of fat in your blood (triglycerides)
- Fluid retention due to cardiac or kidney problems.

Stop using Vagifem and see a doctor immediately
If you notice any of the following when using HRT:

- Migraine-like headaches which happen for the first time
- Yellowing of your skin or the whites of your eyes (jaundice). These may be signs of a liver disease
- A large rise in your blood pressure (symptoms may be headache, tiredness, dizziness)
- Any of the conditions mentioned in the 'Do not use Vagifem' section
- If you become pregnant
- If you notice signs of a blood clot, such as:
  - painful swelling and redness of the legs
  - sudden chest pain
  - difficulty in breathing.

For more information, see 'Blood clots in a vein (thrombosis)'.

The following risks apply to HRT medicines which circulate in the blood. It is not known how these risks apply to locally administered treatments such as Vagifem.

HRT and cancer

Excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the lining of the womb (endometrial cancer)
Taking oestrogen-only HRT tablets for a long time can increase the risk of developing cancer of the womb lining (the endometrium). It is uncertain whether long term (more than one year) or repeated use of local vaginally administered oestrogen products possess a similar risk.

Vagifem has been shown to have very low systemic absorption initially during treatment, and the addition of a progestagen is therefore not necessary.

If you get **breakthrough bleeding** or **spotting,** it's usually nothing to worry about, but you should make an appointment to see your doctor. It could be a sign that your endometrium has become thicker.

Compare
In women who still have a womb and who are not taking HRT, on average, 5 in 1,000 will be diagnosed with endometrial cancer between the ages of 50 and 65.
For women aged 50 to 65 who still have a womb and who take oestrogen-only HRT, between 10 and 60 women in 1,000 will be diagnosed with endometrial cancer (i.e. between 5 and 55 extra cases), depending on the dose and for how long it is taken.

Breast cancer

Evidence suggests that taking combined oestrogen-progestagen and possibly also oestrogen-only HRT increases the risk of breast cancer. The extra risk depends on how long you take HRT. The additional risk becomes clear within a few years. However, it returns to normal within a few years (at most 5) after stopping treatment.
For women who have had their womb removed and who are using oestrogen-only HRT for 5 years, little or no increase in breast cancer risk is shown.

Compare
Women aged 50 to 79 who are not taking HRT, on average, 9 to 17 in 1,000 will be diagnosed with breast cancer over a 5-year period. For women aged 50 to 79 who are taking oestrogen-progestagen HRT over 5 years, there will be 13 to 23 cases in 1,000 users (i.e. an extra 4 to 6 cases).

Regularly check your breasts. See your doctor if you notice any changes such as:
- dimpling of the skin
- changes in the nipple
- any lumps you can see or feel.

Ovarian cancer

Ovarian cancer is rare. A slightly increased risk of ovarian cancer has been reported in women taking HRT for at least 5 to 10 years.

Compare
Women aged 50 to 69 who are not taking HRT, on average, about 2 women in 1,000 will be diagnosed with ovarian cancer over a 5-year period. For women who have been taking HRT for 5 years, there will be between 2 and 3 cases per 1,000 users (i.e. up to 1 extra case).

Effect of HRT on heart and circulation

Blood clots in a vein (thrombosis)
The risk of **blood clots in the veins** is about 1.3- to 3-times higher in HRT users than in non-users, especially during the first year of taking it.
Blood clots can be serious, and if one travels to the lungs, it can cause chest pain, breathlessness, fainting or even death.

You are more likely to get a blood clot in your veins as you get older and if any of the following applies to you. Inform your doctor if any of these situations applies to you:
- you are unable to walk for a long time because of major surgery, injury or illness
- you are seriously overweight (BMI >30 kg/m²)
- you have any blood clotting problem that needs long-term treatment with a medicine used to prevent blood clots
- if any of your close relatives has ever had a blood clot in the leg, lung or another organ
- you have systemic lupus erythematosus (SLE)
- you have cancer.

For signs of a blood clot, see ‘Stop using Vagifem and see a doctor immediately’.

Compare
Looking at women in their 50s who are not taking HRT, on average, over a 5-year period, 4 to 7 in 1,000 would be expected to get a blood clot in a vein.
For women in their 50s who have been taking oestrogen-progestagen HRT for over 5 years, there will be 9 to 12 cases in 1,000 users (i.e. 5 extra cases)
For women in their 50s who have had their womb removed and have been taking oestrogen-only HRT for over 5 years, there will be 5 to 8 cases in 1,000 users (i.e. 1 extra case).

Heart disease (heart attack)
There is no evidence that HRT will prevent a heart attack.
Women over the age of 60 years who use oestrogen-progestagen HRT are slightly more likely to develop heart disease than those not taking any HRT.
For women who have had their womb removed and are taking oestrogen-only therapy there is no increased risk of developing a heart disease.

Stroke
The risk of getting stroke is about 1.5-times higher in HRT users than in non-users. The number of extra cases of stroke due to use of HRT will increase with age.

Compare
Looking at women in their 50s who are not taking HRT, on average, 8 in 1,000 would be expected to have a stroke over a 5-year period. For women in their 50s who are taking HRT, there will be 11 cases in 1,000 users, over 5 years (i.e. 3 extra cases).

Other conditions

HRT will not prevent memory loss. There is some evidence of a higher risk of memory loss in women who start using HRT after the age of 65. Speak to your doctor for advice.

Other medicines and Vagifem
Please tell your doctor or pharmacist if you are using or have recently used any other medicines, including medicines obtained without a prescription. However, Vagifem is not likely to affect other medicines. This is because Vagifem is used for a local treatment in the vagina and contains a very low dose of estradiol.

Pregnancy and breast-feeding
Vagifem is for use in postmenopausal women only. If you become pregnant, stop using Vagifem and contact your doctor.

Driving and using machines
No known effect.

3. How to use Vagifem

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Using this medicine
- You can start using Vagifem on any day which is best for you.
- Insert the vaginal tablet into your vagina with the applicator.

The 'USER INSTRUCTIONS' at the end of the leaflet tell you how to do this. Read the instructions carefully before using Vagifem.

How much to use
- Use one vaginal tablet each day for the first 2 weeks.
- Then use one vaginal tablet twice a week. Leave 3 or 4 days between each dose.

General information about treating symptoms of the menopause
- When using medicines for any menopausal symptoms, it is recommended to use the lowest dose that works, and to use the medicine for as short a time as it is needed.
- Treatment should only be continued if the benefit is greater than the risk. Talk to your doctor about this.

If you use more Vagifem than you should
- If you have used more Vagifem than you should, talk to a doctor or pharmacist.
- Vagifem is for local treatment inside the vagina. The dose of estradiol is so low that a considerable number of tablets would have to be taken to approach the dose normally used for treatment taken by mouth.

If you forget to use Vagifem
- If you forget a dose, use the medicine as soon as you remember.
- Do not use a double dose to make up for a forgotten dose.

If you stop using Vagifem
Do not stop using Vagifem without talking to your doctor. Your doctor will explain the effects of stopping treatment. He or she will also discuss other possibilities for treatment with you.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Common
- Headache
- Stomach pain
- Vaginal bleeding, discharge or discomfort.

Uncommon
- An infection of the genitals caused by a fungus
- Feeling sick (nausea)
- Rash
- Weight increase
- Hot flush
- Hypertension.

Very rare
- Diarrhoea
- Fluid retention
- Migraine aggravated
- Generalised hypersensitivity (e.g. anaphylactic reaction/shock).

The frequency of possible side effects listed above is defined using the following convention:
Very common (affects more than 1 user in 10)
Common (affects 1 to 10 users in 100)
Uncommon (affects 1 to 10 users in 1,000)
Rare (affects 1 to 10 users in 10,000)
Very rare (affects less than 1 user in 10,000)
Not known (frequency cannot be estimated from the available data).

The following side effects can occur with systemic oestrogen treatment:
- Gall bladder disease
- Various skin disorders:
  - discoloration of the skin especially of the face or neck known as 'pregnancy patches' (chloasma)
  - painful reddish skin nodules (erythema nodosum)
  - rash with target-shaped reddening or sores (erythema multiforme).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Vagifem

Keep this medicine out of the sight and reach of children.

Do not refrigerate.

Do not use this medicine after the expiry date which is stated on the carton label and blister after EXP. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.
This medicine may cause risk to the aquatic environment.

6. Contents of the pack and other information

What Vagifem contains

- The active substance is estradiol 10 micrograms (as estradiol hemihydrate). Each vaginal tablet contains 10 micrograms estradiol (as estradiol hemihydrate).
- Other ingredients are: hypromellose, lactose monohydrate, maize starch and magnesium stearate.
- The film-coating contains: hypromellose and macrogol 6000.

What Vagifem looks like and contents of the pack

Each white vaginal tablet comes in an applicator which is used once only.

Vagifem is engraved with NOVO 278 on one side.

Pack sizes:
18 vaginal tablets with applicators.
24 vaginal tablets with applicators.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

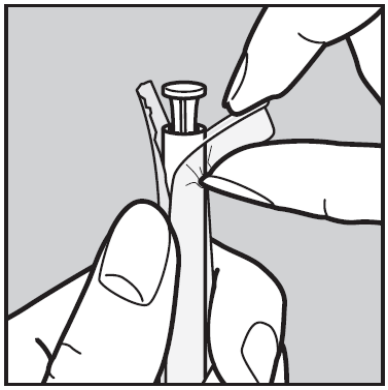
This leaflet was last revised in:

Other sources of information

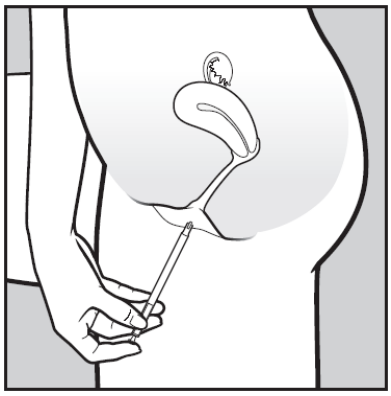
Detailed information on this medicine is available on the website of {MS/Agency}

USER INSTRUCTIONS

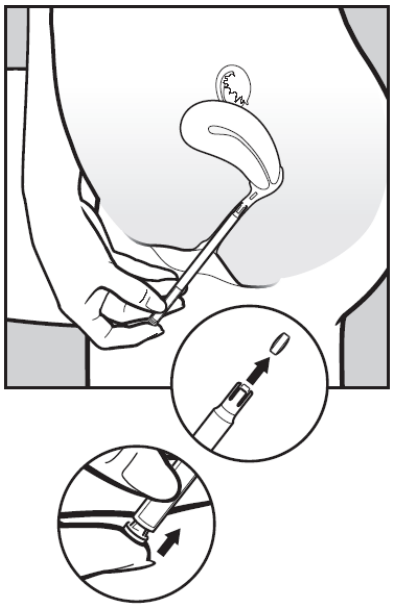
How to use Vagifem



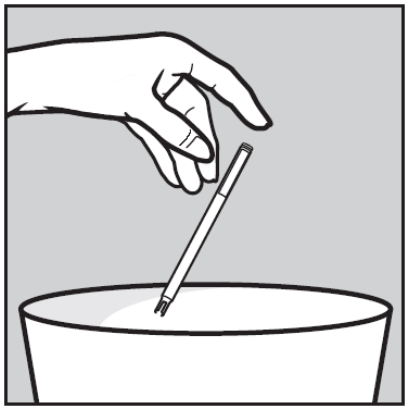
1. Tear off one single blister pack.
   Open the end as shown in the picture.



2. Insert the applicator carefully into the vagina.
   Stop when you can feel some resistance (8–10 cm).



3. To release the tablet, gently press the push-button until you feel a click.
   The tablet will stick to the wall of the vagina straight away.
   It will not fall out if you stand up or walk.



4. Take out the applicator and throw it away.