Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vagifem 25 micrograms Vaginal Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: One vaginal tablet contains Estradiol hemihydrate equivalent to estradiol 25 micrograms.

Excipients: lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Vaginal Tablet

Product imported from Italy:
White, biconvex film-coated vaginal tablet marked 'NOVO 279' on one side and inset in a disposable applicator

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the treatment of atrophic vaginitis due to estrogen deficiency.

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

4.2 Posology and method of administration

Dosage

The usual dosage is one tablet (containing 25 micrograms estradiol) daily for 2 weeks followed by a maintenance dose of one tablet twice a week. Treatment should be limited to as short a period as possible.

Administration

For intravaginal administration only, using the supplied applicator. Each applicator with insert tablet is intended for single use only.

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 section 4.4, Special warnings and precautions for use*) should be used.

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

During treatment, especially during the first two weeks, minimal absorption may be seen but as plasma oestradiol levels after the first two weeks usually do not exceed postmenopausal levels the addition of a progestogen is not recommended.

4.3 Contraindications

1. Known, past or suspected breast cancer.
2. Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer).
3. Undiagnosed genital bleeding.
4. Untreated endometrial hyperplasia.
5. Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism).
6. Known hypersensitivity to the active substance or to any of the excipients.
7. 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 annually and HRT should only be continued as long as the benefit outweighs the risk.

Medical examination/follow-up

Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breasts) 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 mammography should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Vaginal infections should be treated before initiation of Vagifem therapy.

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 systemic oestrogen treatment, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- A history of, or 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

Due to the local administration of low dose estradiol in Vagifem, the recurrence or aggravation of the above-mentioned conditions as well as the occurrence of the conditions mentioned below is less likely than with systemic oestrogen treatment.

Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contra-indication 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

The risk of endometerial hyperplasia and carcinoma is increased when unopposed systemic oestrogens are administered for prolonged periods of time. The endometrial safety of long-term or repeated use of low-dose topical vaginal oestrogens has not been evaluated and the potential for endometrial hyperstimulation cannot be ruled out. As with all HRT preparations breakthrough bleeding and spotting while using Vagifem should be investigated to exclude endometrial malignancy. While patients are receiving this medication, they should be reviewed by their doctor regularly at least every six to twelve months. During follow-up of patients who receive repeat or long-term treatment with Vagifem, special consideration should be given to symptoms of endometrial hyperstimulation or malignancy.

Breast Cancer

A randomised placebo-controlled trial, the Women's Health Initiative study (WHI) and epidemiological studies, including the Million Women Study (MWS), have reported an increased risk of breast cancer in women taking oestrogens, oestrogen-progestogen combinations or tibolone for HRT for several years (see Section 4.8). For all HRT, an excess risk becomes apparent within a few years of use and increases with duration of intake but returns to baseline within a few (at most five) years after stopping treatment.

In the MWS, the relative risk of breast cancer with conjugated equine oestrogens (CEE) or estradiol (E2) was greater when a progestogen was added, either sequentially or continuously, and regardless of type of progestogen. There was no evidence of a difference in risk between the different routes of administration.

In the WHI study, the continuous combined conjugated equine oestrogen and medroxyprogesterone acetate (CEE + MPA) product used was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases compared to placebo.

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

Venous thromboembolism

Systemic HRT is associated with a higher relative risk of developing venous thormboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomised controlled trial and epidemiological studies found a two – to threefold higher risk for users compared with non-users. For non-users it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged between 60-69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5 years period will be between 2 and 6 (best estimate =4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate =9) per 1000 women aged 60-69 years. The occurrence of such an event is more likely in the first year of HRT than later.

Generally recognised risk factors for VTE include a personal history or family history, severe obesity (BMI > 30 Kg/m^2) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.

Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. Personal or strong family history of thromboembolism, or recurrent spontaneous abortion, should be investigated in order to exclude a thormbophilic predisposition. Until a thorough evaluation of thormbophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

The risk of VTE may be temporarily increased with prolonged immobilization, major trauma or major surgery. As in all postoperative patients scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT 4 to 6 weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised.

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 cardiovascular benefit with continuous combined conjugated oestrogens and medroxyprogesterone acetate (MPA). Two large clinical trials (WHI and HERS i.e. Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomised controlled trials examining effects in cardiovascular morbidity or mortality. Therefore it is uncertain whether these findings also extend to other HRT products.

Stroke

One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated oestrogens and MPA. For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5 –year period is about 3 per 1000 women aged 50-59 years and 11 per 1000 women aged 60-69 years. It is estimated that for women who use conjugated oestrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate =1) per 1000 users aged 50-59 and between 1 and 9 (best estimate =4) per 1000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products.

Ovarian cancer

Use of estrogen alone and estrogen plus progestogen therapies for at least 5 or 10 years has been associated with an increased risk of ovarian cancer in some epidemiological studies.

Other conditions

- Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed during the first weeks of treatment. Patients with terminal renal insufficiency should also be closely observed, since it is expected that the level of circulating active ingredient in Vagifem is increased.

- 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.

- Oral 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 radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. cortcoid 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). With vaginal administration, stimulation of the liver by the first-pass effect is avoided and thus, transvaginal oestrogens might affect hormone binding proteins and other serum proteins produced by the liver less than oral hormones.

- There is no conclusive evidence for improvement of cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined CEE and MPA after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products.

4.5 Interaction with other medicinal products and other forms of interaction

To-date, interactions between Vagifem and other concomitantly administered drugs have not been reported. However, the serum concentration and efficacy of oestrogens could be reduced and their metabolism increased by concomitant administration of drugs known to induce drug metabolising enzymes, specifically CYP 450 enzymes, such as 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 raise the metabolism of oestrogens and progestogens.

With intravaginal administration, the first-pass effect in the liver is avoided and thus, estradiol given intravaginally might be less affected by enzyme inducers than oral hormones.

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.

Vagifem is not indicated during lactation.

4.7 Effects on ability to drive and use machines

No effects known.

4.8 Undesirable effects

More than 640 patients have been treated with Vagifem in clinical trials, including over 200 patients treated for between 28 and 64 weeks. Well known oestrogen-related adverse effects which occurred with a higher frequency in the treated group as compared with the placebo group are presented as "Common (>1/100, <1/10).

The spontaneous reporting rate on Vagifem corresponds to approximately 1 case per 10,000 patient years. Adverse events for which an increased frequency has not been observed in clinical trials, but which have been spontaneously reported and which on an overall judgement are considered possibly related to Vagifem treatment and therefore presented as "Very rare (<1/10,000).

Post marketing experience is subject to under-reporting especially with regard to trivial and well-known adverse drug reactions. The presented frequencies should be interpreted in that light.

The most commonly reported adverse drug reactions are: vaginal discharge and vaginal discomfort. Oestrogen-related adverse events such as breast pain, peripheral oedema and postmenopausal bleedings are most likely to present at the beginning of Vagifem treatment.

System organ class	Common >1/100; <1/10	Uncommon >1/1000; <1/100	Rare >1/10,000; <1/1000	Very rare <1/10,000 incl. Isolated reports
Infections and infestations	Genital candidiasis or vaginitis, see also "Reproductive system and breast disorders"			
Neoplasms benign and malignant (incl,. Cysts and polyps)				Breast cancer* Endometrial cancer
Immune system disorders				Hypersensitivity, NOS
Metabolism and nutrition disorders				Fluid retention, see also "General disorders and adminstration site conditions"
Psychiatric disorders				Insomnia Depression
Nervousness system disorders	Headache			Migraine aggravated
Vascular disorders				Deep venous thrombosis
Gastrointestinal disorders	Nausea abdominal pain, abdominal distension or abdominal discomfort Dyspepsia Vomiting Flatulence			Diarrhoea
Skin and subcutaneous tissue disorders				Urticaria Rash erythematous Rash NOS Rash pruritic General pruritus

Reproductive system and breast disorders	Vaginal haemorrhage, vaginal discharge or vaginal discomfort Breast oedema, breast enlargement, breast pain or breast tenderness			Hyperplasia endometrial Vaginal irritation, vaginal pain, vaginismus, vaginal ulceration, see also "Infections and infestations"
General disorders and administration site conditions	Oedema peripheral			Drug ineffective
Investigations				Weight increased Blood oestrogen increased

According to evidence from a large number of epidemiological studies and one randomized placebo-controlled trial, the Women's Health Initiative (WHI), the overall risk of breast cancer increases with increasing duration of HRT use in current or recent HRT users.

For *oestrogen-only* HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which >80% of HRT use was oestrogen-only HRT) and from the epidemiological Million Women Study (MWS) are similar at 1.35 (95% CI: 1.21-1.49) and 1.30 (95% CI: 1.21-1.40), respectively.

For *oestrogen plus progestogen* combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with oestrogens alone.

The MWS reported that, compared to never users, the use of various types of oestrogen-progestogen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95% CI: 1.88-2.12) than use of oestrogens alone (RR = 1.30, 95% CI: 1.21-1.40) or use of tibolone (RR = 1.45, 95% CI: 1.25-1.68).

The WHI trial reported a risk estimate of 1.24 (95% CI: 1.01-1.54) after 5.6 years of use of oestrogen-progestogen combined HRT (CEE + MPA) in all users compared with placebo.

The absolute risks calculated from the MWS and the WHI trial are presented below:

The MWS has estimated, from the known average incidence of breast cancer in developed countries, that:
For women not using HRT, about 32 in every 1000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years.
For 1000 current or recent users of HRT, the number of additional cases during the corresponding period will be
For users of *oestrogen-only* replacement therapy, between 0 and 3 (best estimate = 1.5) for 5 years' use between 3 and 7 (best estimate = 5) for 10 years' use.
For users of *oestrogen plus progestogen* combined HRT, between 5 and 7 (best estimate = 6) for 5 years' use between 18 and 20 (best estimate = 19 for 10 years' use.

The WHI trial estimated that after 5.6 years of follow-up of women between the ages of 50 and 79 years, an *additional* 8 cases of invasive breast cancer would be due to *oestrogen-progestogen combined* HRT (CEE + MPA) per 10,000 women years. According to calculations from the trial data, it is estimated that:
For 1000 women in the placebo group, about 16 cases of invasive breast cancer would be diagnosed in 5 years.
For 1000 women who used oestrogen + progestogen combined HRT (CEE + MPA), the number of additional cases would be between 0 and 9 (best estimate = 4) for 5 years' use.

The number of additional cases of breast cancer in women who use HRT is broadly similar for women who start HRT irrespective of age at start of use (between the ages of 45-65) (*see section 4.4, Special warnings and precautions for use*).

Endometrial cancer

In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed oestrogens. According to data from epidemiological studies, the best estimate of the risk is that for women not using HRT, about 5 in every 1000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and oestrogen dose, the reported increase in endometrial cancer risk among unopposed oestrogen users varies from 2- to 12- fold greater compared with non-users. Adding a progestogen to oestrogen-only therapy greatly reduces this increased risk.

The following adverse reactions have been reported in association with other oestrogen treatment:
Myocardial infarction, congestive heart disease
Gallbladder disease
Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura, pruritus
Vaginal candidiasis
Risk of development of endometrial cancer (*see section 4.4, Special warnings and precautions for use*), endometrial hyperplasia or increase in size of uterine fibroids*
Insomnia
Epilepsy
Libido disorders NOS (not otherwise specified)
Deterioration of asthma
Probable dementia (*see section 4.4, Special warnings and precautions for use*).

*In non-hysterectomised women

4.9 Overdose

No cases of overdosing has been reported. Vagifem is intended for local treatment intra-vaginally. The dose of 17β-estradiol (25µg) is so low that a considerable number of tablets would have to be ingested to approach the dose normally used for oral systemic treatment. There is no specific antidote and treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code G03C A03.

Natural and semisynthetic oestrogens, plain (for vaginal use).

The estrogen, 17β−estradiol, contained in Vagifem is chemically and biologically identical to the endogenous human 17β−estradiol and is therefore classified as a human estrogen.

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 estrogen receptors. The steroid receptor complex is bound to the cell's DNA and induces synthesis of specific proteins.

Maturation of the vaginal epithelium is dependent upon estrogen. Estrogen increases the number of superficial and intermediate cells as compared to basal cells. Estrogen keeps pH in the vagina down to around 4.5 which enhances normal bacterial flora, Lactobacillus Doderlein predominating.

5.2 Pharmacokinetic properties

Oestrogen drug products are well absorbed through the skin, mucous membranes, and the gastrointestinal tract. The Vaginal delivery of oestrogens circumvents 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 25 µg E2 tablet . Subjects were randomized 1:1 to receive either 25 µg E2 (Vagifem) or 10 µg E2. Plasma levels of oestradiol (E2), oestrone (E1) and oestrone sulfate (E1S) were determined at Day -1 (pre-dose), Day 1 (after 1st dosing), Day 14 (after 14 days of once-daily dosing), Day 82 (pre-dose after 10 weeks twice-weekly treatment) and Day 83 (post-dose after 10 weeks twice-weekly treatment). The primary bioavailability endpoint of the clinical trial was AUC(0-24) for plasma E2 levels (see Table 1): this parameter indicated higher systemic oestradiol levels for Vagifem 25 µg as compared to baseline on treatment days 1, 14 and 83. However, average plasma E2 levels (Cave(0-24)) at all time points overall remained below 20 pg/ml. The data from day 82 indicate that in the long term, systemic oestradiol levels do not accumulate during twice weekly maintenance therapy (see Table 1).

Table 1 Values of PK parameters from plasma Oestradiol (E2) concentrations: Study VAG-1850

	$AUC_{(0-24)}$ pg.h/mL(geom. mean)	**$C_{ave(0-24)}$ pg/mL (geom.mean)**
Day -1	96.66	4.03
Day 1	476.14	19.84
Day 14	438.87	18.29
Day 82	48.13	2.01
Day 83	225.94	9.41

The levels of oestrone seen during 12 weeks of Vagifem 25 µg administration do not show any accumulation of oestrone.

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

5.3 Preclinical safety data

As 17β−estradiol is a well−known substance in humans, described in the pharmacotoxicological literature, no further studies have been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose
Lactose Monohydrate
Maize Starch
Magnesium Stearate

Film-coating:
Hypromellose
Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25ºC. Do not refrigerate. Keep the container in the outer carton in order to protect from light.

6.5 Nature and contents of container

Each Vagifem tablet is contained in a single-use HD-polyethylene/polypropylene applicator. Each applicator with inset tablet is packed separately in a laminated blister pack consisting of aluminium foil and polyvinylchloride foil.
Pack size: 15 tablets inset in applicators.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

B & S Healthcare
Unit 4, Bradfield Road
Ruislip
Middlesex HA4 0NU
United Kingdom

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1328/161/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st October 2011

10 DATE OF REVISION OF THE TEXT