

**Public Assessment Report**  
**Decentralised Procedure**

**VAGIFEM 10 MICROGRAMS VAGINAL TABLETS**

**UK/H/2176/001/DC**  
**UK licence no: PL 04668/0237**

**Novo Nordisk AS**

# VAGIFEM 10 MICROGRAMS VAGINAL TABLETS

## LAY SUMMARY

On 18<sup>th</sup> January 2010, Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Lichtenstein, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Slovak Republic, Spain, Sweden and the UK agreed to grant a Marketing Authorisation to Novo Nordisk for the medicinal product Vagifem 10 micrograms Vaginal Tablets. The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, a licence was granted in the UK on 17<sup>th</sup> February 2010.

Vagifem 10 micrograms Vaginal Tablets 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 estrogen in your body. This happens naturally after the menopause. This product works by replacing the estrogen which is normally produced in the ovaries of women. It is inserted into your vagina, so the hormone is released where it is needed.

The active ingredient estradiol hemihydrate is a female sex hormone that belongs to a group of hormones called estrogens, and works in exactly the same way as the estradiol produced by the ovaries of a woman.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Vagifem 10 micrograms Vaginal Tablets outweigh the risks, hence a Marketing Authorisation has been granted.

## TABLE OF CONTENTS

Module 1: Information about initial procedure	Page 3
Module 2: Summary of Product Characteristics	Page 4
Module 3: Product Information Leaflets	Page 22
Module 4: Labelling	Page 24
Module 5: Scientific Discussion	Page 28
1 Introduction	
2 Quality aspects	
3 Non-clinical aspects	
4 Clinical aspects	
5 Overall conclusions	
Module 6	Steps taken after initial procedure

## Module 1

<b>Product Name</b>	Vagifem 10 microgram Vaginal Tablets
<b>Type of Application</b>	Article 8.3, Full dossier
<b>Active Substance</b>	Estradiol hemihydrate
<b>Form</b>	Vaginal tablets
<b>Strength</b>	10 micrograms
<b>MA Holder</b>	Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark
<b>RMS</b>	UK
<b>CMS</b>	Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Lichtenstein, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Slovak Republic, Spain and Sweden
<b>Procedure Number</b>	UK/H/2176/001/DC
<b>Timetable</b>	Day 210 – 18 <sup>th</sup> January 2010

## Module 2

# 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 a 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 using the applicator.

Initial dose: One vaginal tablet daily for two weeks.

Maintenance dose: One vaginal tablet twice a week.

Treatment may be started on any convenient day.

If a dose is forgotten, it should be 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.

A switch to the higher dose product Vagifem 25 micrograms should be considered if the response after three months is insufficient for satisfactory symptom relief.

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

During treatment, especially during the first two weeks of daily administration, minimal systemic absorption may occur but as plasma estradiol levels usually do not exceed normal postmenopausal levels the addition of a progestagen is not recommended.

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 idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- 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 reinstating 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 mammography should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

##### 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. 1<sup>st</sup> 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 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

Women with intact uterus with abnormal bleeding of unknown aetiology or women with an intact uterus who have previously been treated with unopposed oestrogens should be examined with special care in order to exclude hyperstimulation/malignancy of the endometrium before initiation of treatment with Vagifem.

The risk of endometrial cancer after treatment with oral unopposed oestrogens is dependent on both duration of treatment and on oestrogen dose. The dose of estradiol in Vagifem is very low and treatment is local. A minor degree of systemic absorption may occur in some patients, especially during the first two weeks of once daily administration (see section 5.2). No systemic effect is expected during the local oestrogen treatment with Vagifem, and the addition of a progestagen is not recommended.

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 on 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.

*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.*

#### Breast cancer

Systemic oestrogen or oestrogen-progestagen treatment may increase the risk of breast cancer. Relative risk of breast cancer with conjugated equine oestrogens or estradiol was greater when a progestagen was added, either sequentially or continuously, and regardless of type of progestagen. A large randomised clinical trial (WHI trial) showed no increase in breast cancer incidence in hysterectomised postmenopausal women treated with conjugated equine oestrogen alone.

#### Venous thromboembolism

Systemic HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism.

In the oestrogen alone sub-study of WHI, the risk of VTE (DVT and pulmonary embolism (PE)) was reported to be increased for women receiving daily conjugated equine oestrogens (CEE) compared to placebo (30 versus 22 per 10,000 women-years). The occurrence of such an event is more likely in the first year of treatment than later.

Generally recognised risk factors for VTE include a personal history or family history, severe obesity (BMI > 30 kg/m<sup>2</sup>) and systemic lupus erythematosus (SLE). The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major 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 prior to surgery, 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 experience a potential thromboembolic symptom (e.g., painful swelling of a leg, sudden pain in the chest, dyspnea). Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

#### Coronary artery disease (CAD)

There is no evidence from randomised controlled trials that oestrogens or combined oestrogen-progestagen protect against coronary artery disease.

#### Stroke

In the WHI estrogen alone sub-study, a statistically significant increased risk of stroke was reported in women receiving daily conjugated oestrogens (CE 0.625 mg) compared to placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated after the first year of treatment and persisted.

#### Ovarian cancer

Use of systemic oestrogen alone and oestrogen plus progestagen therapies for at least 5-10 years has been associated with a slightly 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.

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 postmenopausal women or other HRT products.

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

#### 4.5 Interaction with other medicinal products and other forms of interaction

Due to a local administration of the very low dose of estradiol in Vagifem, systemic interactions of clinical relevance are not expected.

#### 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 effect.

##### 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
<b>Infections and infestations</b>		Vulvovaginal mycotic infection	
<b>Nervous system disorders</b>	Headache		
<b>Gastrointestinal disorders</b>	Abdominal pain	Nausea	
<b>Reproductive system and breast disorders</b>	Vaginal haemorrhage, vaginal discharge or vaginal discomfort		
<b>Skin and subcutaneous tissue disorders</b>		Rash	
<b>Investigations</b>		Weight increased	
<b>Vascular disorders</b>		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 (incl. 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 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 systemic oestrogen treatment:

- 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 (see section 4.4).

#### 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 17 $\beta$ -estradiol, is chemically and biologically identical to endogenous human estradiol.

Endogenous 17 $\beta$ -estradiol induces and maintains the primary and secondary female sexual characteristics. The biological effect of 17 $\beta$ -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 dependant 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-month double-blind, randomized, parallel group, placebo-controlled multicenter 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, normalization 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, multicenter 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 randomized 1:1 to receive either 10 micrograms or 25 micrograms Vagifem. Plasma levels of estradiol (E2), oestrone (E1) and oestrone sulphate (E1S) were determined.  $AUC_{(0-24)}$  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 sulphate after 12 weeks of Vagifem 10 micrograms administration did not exceed baseline levels, i.e., no accumulation of oestrone or oestrone sulphate 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 oestriol, which is the major urinary metabolite. In postmenopausal women, a significant portion of the circulating oestrogens exist as sulphate conjugates, especially oestrone sulphate, which serves as a circulating reservoir for the formation of more active oestrogens.

### *Elimination*

Estradiol, oestrone and oestriol 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

$17\beta$ -Estradiol is a well-known substance. Nonclinical 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 packs contain 3 blister cards of 6 applicators with inset tablets. 24 packs contain 4 blister cards of 6 applicators with inset tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

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

**7 MARKETING AUTHORISATION HOLDER**

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

The registered office in the UK is:-  
Novo Nordisk Ltd  
Broadfield Park  
Brighton Road  
Crawley  
West Sussex  
RH11 9AT

Tel: 01293 613555

**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**

17/02/2010

# Module 3



## PACKAGE LEAFLET: INFORMATION FOR THE USER

### Vagifem® 10 micrograms

vaginal tablets  
Estradiol

Read all of this leaflet carefully, before you start using this medicine.

- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet please tell your doctor or pharmacist.

#### In this leaflet:

1. What Vagifem® is and what it is used for
2. Before you use Vagifem®
3. How to use Vagifem®
4. Possible side effects
5. How to store Vagifem®
6. Further information

#### 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 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.

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

#### 2. Before you use Vagifem®

##### Medical check-ups

Before you start using Vagifem®, your doctor will tell you about the risks and benefits of the treatment (see also Section 4). You should only take hormones for those menopausal symptoms that have a negative impact on your quality of life. Before you start using Vagifem® and regularly during treatment, your doctor will check whether Vagifem® is the right treatment for you. Your doctor should check at least once a year and discuss with you if it is right for you to continue the treatment. Your doctor will consider your general state of health. If you have a close relative (e.g. mother, sister, maternal or paternal grandmother), who has suffered from any serious illness such as blood clots or breast

cancer, you might be at a higher risk for serious illness. Always tell your doctor about any close relative(s) suffering from serious illness.

As well as regular check-ups with your doctor, you should:

- Regularly examine your breasts for any changes, such as dimpling or sinking of the skin, changes in the nipple, or any lumps you can see or feel. Tell your doctor if you notice any changes.
- Go for regular breast screening (mammography) and cervical smear tests depending on your doctor's advice.

#### Do not use Vagifem® if:

- You are allergic (hypersensitive) to estradiol or any of the other ingredients of Vagifem® (listed in Section 6 below)
- You have or have ever had, or think you might have breast cancer
- You have or have ever had, or think you might have a hormone dependent tumour, e.g. endometrial cancer (cancer of the lining of the womb)
- You have vaginal bleeding which has not been diagnosed
- You have excessive growth of the lining of the womb (endometrial hyperplasia) and you are not being treated for it
- You have or previously have had a blood clot inside the blood vessels of the legs or lungs (deep vein thrombosis or pulmonary embolism)
- You have recently had a heart attack, stroke or have chest pain (angina)
- You have or have had a liver disease and your liver tests have not returned to normal
- You have porphyria. This is a rare disease which affects the production of some of your blood pigments.

Do not use Vagifem® if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before using this medicine.

#### Take special care with Vagifem®

Check with your doctor before using Vagifem® if you have or have ever had any of the conditions in the list below. Your doctor may want to follow you more closely. It is less likely that the conditions mentioned below will get worse or come back. This is because Vagifem® is taken by local administration (treatment that affects only one part of the body) as opposed to systemic (treatment that affects the whole body).

- Asthma
- Epilepsy
- Diabetes
- Gallstones
- High blood pressure
- Migraines or severe headaches
- Liver problems such as 'liver adenoma' (a benign tumour)
- History of endometrial hyperplasia (thickening of the lining of your womb)
- Otosclerosis. This is when you lose your hearing over a period of time
- Systemic lupus erythematosus (a disease affecting the skin, joints and kidneys)
- Risk factors for oestrogen dependent tumours, e.g. 1st degree heredity for breast cancer
- Risk factors for blood clots (see Section 4 "Other side effects of systemic HRT")
- Leiomyoma (benign tumours of the womb) or endometriosis

(growth of the womb lining outside the womb).

If any of the above applies to you, or if you are not sure, talk to your doctor or pharmacist before using Vagifem®.

#### Using other medicines

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

- Do not use Vagifem® if you are pregnant, or if you are breast-feeding
- If you get pregnant while you are using Vagifem®, stop using it and see a doctor straight away.

#### Driving and using machines

No known effect.

#### 3. How to use Vagifem®

Always use Vagifem® exactly as your doctor has told you. You should 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 more 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 product, ask your doctor or pharmacist.

#### 4. Possible side effects

Like all medicines, Vagifem® can cause side effects, although not everybody gets them.

Stop using Vagifem® and see a doctor straight away if you notice any of the following side effects:

- A migraine-type headache you have not had before
- Yellow colouring of your skin or eyes (jaundice) or other liver problems
- A big increase in blood pressure
- Blood clots called "deep vein thrombosis" (see also "Other side effects of systemic HRT")
- If you develop any of the illnesses listed in Section 2 "Before you use Vagifem®"

Tell your doctor or pharmacist if any of the following side effects get serious or last longer than a few days:

#### Common

May affect 1 to 10 users in 100

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

#### Uncommon

May affect 1 to 10 users in 1,000

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

#### Very rare

May affect less than 1 user in 10,000

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

#### Side effects of HRT

Vagifem® is used for local treatment in the vagina and contains only a small amount of estradiol. This means that the chances of getting the diseases described below are less likely than with HRT products used for systemic treatment (treatment that affects the body as a whole).

#### The following side effects can occur with systemic oestrogen treatment:

- Myocardial infarction, congestive heart disease
- Stroke
- Gall bladder disease
- Skin disorders including brown patches in the face, skin rashes including red inflammation on the hands or the legs (erythema multiforme), a bruise-like rash and itching
- Risk of excessive growth of the lining of the womb (endometrial hyperplasia) and developing endometrial cancer (cancer of the lining of the womb) or an increase in size of fibroids (benign lumps) in the womb
- Being unable to sleep (insomnia)
- Epilepsy
- Loss of sex drive (libido)
- Deterioration of asthma
- Loss of memory and other mental powers (dementia).

#### Other side effects of systemic HRT

#### Endometrial hyperplasia (excessive growth of the lining of the womb) and endometrial cancer (cancer of the lining of the womb)

It has been known that in women who still have their womb taking

8-2791-01-001-1

systemic oestrogens alone for long periods of time increases the risk of excessive growth of the lining of the womb (endometrial hyperplasia) and of developing endometrial cancer (cancer of the lining of the womb). Taking a hormone called progestagen for at least part of your cycle, in combination with the systemic oestrogen, helps greatly to reduce this additional risk.

If you experience vaginal bleeding or spotting during treatment with Vagifem®, you should contact your doctor who will ask you to undergo examinations to investigate the reason.

Vagifem® has not been shown to increase the risk of endometrial hyperplasia or cancer of the endometrium, and the addition of progestagen is therefore not recommended.

**Breast cancer**

Clinical studies have shown that systemic oestrogen or oestrogen-progestagen may increase the risk of breast cancer. The WHI trial (a large clinical study) showed no increase in the risk of breast cancer in postmenopausal women who have had their womb removed (have had prior hysterectomy) and who were taking oral oestrogen alone.

To be able to detect a breast tumour as early as possible, it is important to regularly examine your breasts for any changes and to discuss any changes with your doctor. Also go for regular health check, including mammography. If you are anxious about the risk of breast cancer, you should talk to your doctor about the risks and benefits of HRT.

**Blood clots in the deep veins**

Every woman is at risk of getting a blood clot whether or not she takes HRT.

Systemic HRT may increase the risk of blood clots in the veins up to 3 times, especially in the first year of taking it.

If you think you are suffering from a blood clot, **stop using Vagifem® and see a doctor straight away.**

The signs include:

- Pain and swelling in your leg
- Sudden chest pain
- Difficulty breathing.

You are more likely to get a blood clot if:

- You are very overweight
- You have had a blood clot in the past
- You have had any blood clotting problems that need treatment with a medicine such as warfarin
- Any of your close family has had blood clots
- You have had a miscarriage
- You are off your feet for a long time due to surgery, injury or illness
- You have Systemic Lupus Erythematosus (an autoimmune disease affecting the skin, joints and kidneys).

**Stroke**

There is a slightly higher risk of having a stroke if you are taking systemic HRT.

Other factors that increase the risk of stroke are:

- Getting older
- High blood pressure
- Smoking
- Drinking too much alcohol
- An irregular heartbeat.

If you get migraine-type headaches, with or without disturbed or blurred vision, **stop using HRT and see a doctor as soon as possible.**

**Ovarian cancer**

Use of systemic oestrogen alone and oestrogen plus progestagen therapies for at least 5 or 10 years have been associated with an increased risk of ovarian cancer in some epidemiological studies.

**Dementia**

There is some evidence for an increased risk of dementia in women older than 65 years, who were using systemic oestrogen-progestagen combination.

**Gall bladder disease**

Gall bladder disease has been reported after treatment with systemic oestrogen-progestagen.

**Effects on the skin**

Brown patches on the face, skin rashes including red inflammation on the hands or the legs (erythema multiforme) or a bruise-like rash have been reported after treatment with HRT.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**5. How to store Vagifem®**

Keep out of the reach and sight of children.

Do not refrigerate.

Do not use Vagifem® 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

**6. Further 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 content 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 Bagsvaerd  
Denmark  
Tel: + 45 44 44 88 88  
Fax: + 45 44 49 05 55

The registered office in the UK is:-  
Novo Nordisk Limited  
Broadfield Park  
Brighton Road  
Crawley  
West Sussex  
RH11 9RT

Tel: (01293) 613555

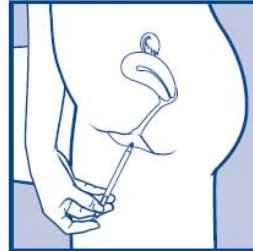
**This leaflet was last approved in:**

**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.



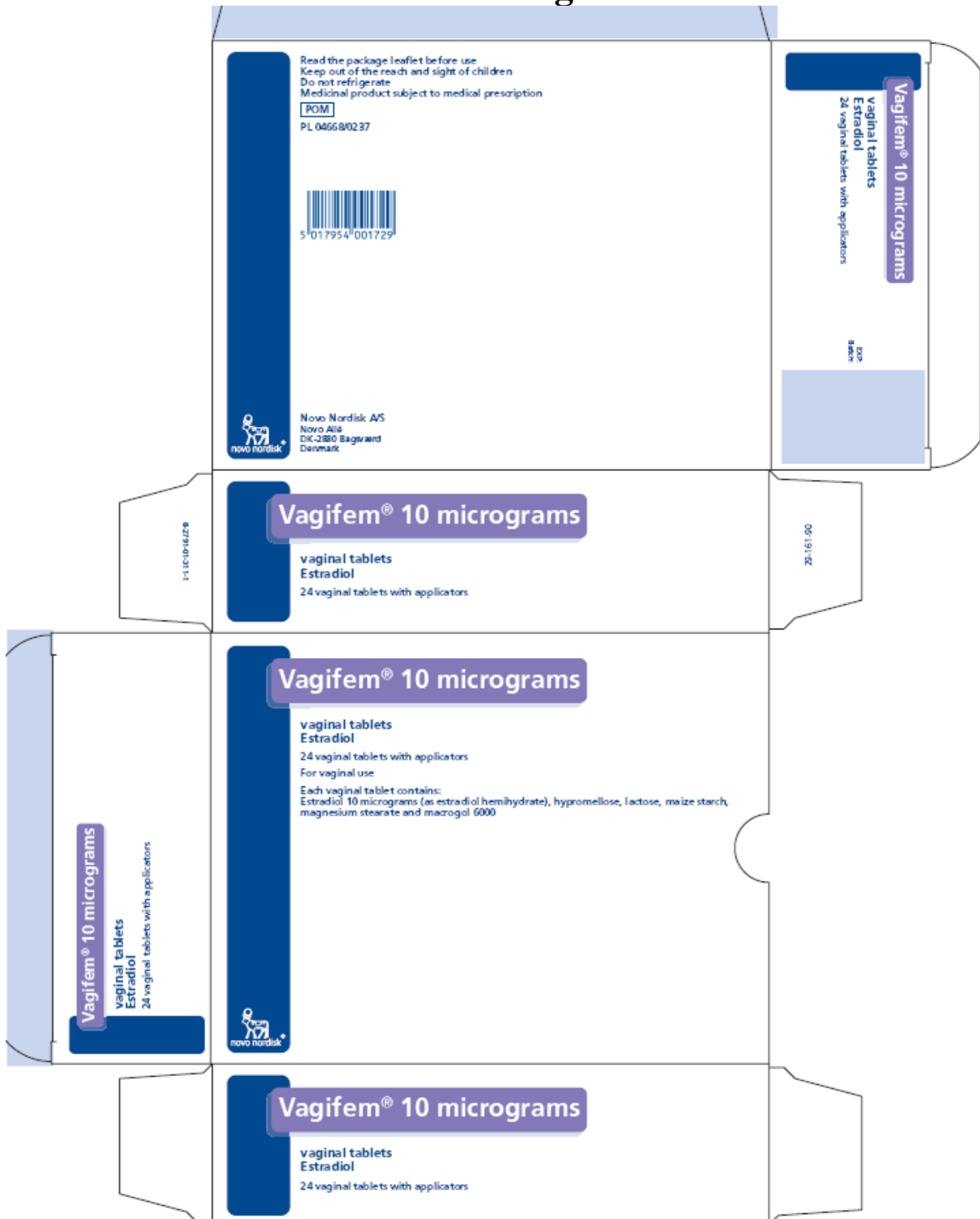
4. Take out the applicator and throw it away

Vagifem® is a registered trademark owned by Novo Nordisk FemCare AG, Switzerland

© 2010  
Novo Nordisk A/S



# Module 4 Labelling



	<p>■ Vagifem® 10 micrograms vaginal tablets Estradiol For vaginal use</p>		<p>EXP: Batch:</p>	---
	<p>Vagifem® 10 micrograms vaginal tablets Estradiol For vaginal use</p>		<p>EXP: Batch:</p>	---
	<p>Vagifem® 10 micrograms vaginal tablets Estradiol For vaginal use</p>		<p>EXP: Batch:</p>	---
	<p>Vagifem® 10 micrograms vaginal tablets Estradiol For vaginal use</p>		<p>EXP: Batch:</p>	---
Z791-01-01	<p>Vagifem® 10 micrograms vaginal tablets Estradiol For vaginal use</p>		<p>EXP: Batch:</p>	---
	<p>Vagifem® 10 micrograms vaginal tablets Estradiol For vaginal use</p>		<p>EXP: Batch:</p>	---
	<p>Vagifem® 10 micrograms vaginal tablets Estradiol For vaginal use</p>		<p>EXP: Batch:</p>	---
	<p>Vagifem® 10 micrograms vaginal tablets Estradiol For vaginal use</p>		<p>EXP: Batch:</p>	---
	<p>Vagifem® 10 micrograms vaginal tablets Estradiol For vaginal use</p>		<p>EXP: Batch:</p>	---
	<p>Vagifem® 10 micrograms vaginal tablets Estradiol For vaginal use</p>		<p>EXP: Batch:</p>	---
	<p>Vagifem® 10 micrograms vaginal tablets Estradiol For vaginal use</p>		<p>EXP: Batch:</p>	---
	<p>Vagifem® 10 micrograms vaginal tablets Estradiol For vaginal use</p>		<p>EXP: Batch:</p>	---

## **Module 5**

### **Scientific discussion during initial procedure**

#### **I INTRODUCTION**

On 18<sup>th</sup> January 2010, Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Lichtenstein, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Slovak Republic, Spain, Sweden and the UK agreed to grant a Marketing Authorisation to Novo Nordisk for the medicinal product Vagifem 10 micrograms Vaginal Tablets. The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, a licence was granted in the UK on 17<sup>th</sup> February 2010.

This application was made under Article 8.3 of Directive 2001/83 EC for Vagifem 10 micrograms Vaginal Tablets, containing the known active substance estradiol hemihydrate.

The estrogen component 17 $\beta$ -estradiol is identical to endogenous human estradiol. 17 $\beta$ -estradiol compensates for the reduced levels of estrogens in postmenopausal women and reduces the vaginal atrophy related to estrogen deficiency. Estradiol vaginal tablets are intended for use in postmenopausal women, with or without an intact uterus. The tablets are administered intravaginally using an applicator.

As Vagifem 10microgram Vaginal Tablets have not been marketed in any country prior to this application, a risk management plan was submitted by the applicant. There are no new identified risks. Routine risk minimization activities are sufficient to cover important identified risks, important potential risks and important missing information. These activities include the spontaneous reporting system, literature surveillance, periodic safety reporting, and risk communication via product information.

A suitable pharmacovigilance system was submitted with this application.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.



**II. ABOUT THE PRODUCT**

Name of the product in the Reference Member State	Vagifem 10 microgram Vaginal Tablets
Name(s) of the active substance(s) (USAN)	Estradiol hemihydrate
Pharmacotherapeutic classification (ATC code)	Natural and semisynthetic estrogens, plain (G03CA03)
Pharmaceutical form and strength(s)	Vaginal tablets 10 micrograms
Reference numbers for the Mutual Recognition Procedure	UK/H/2176/001/DC
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Lichtenstein, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Slovak Republic, Spain and Sweden
Marketing Authorisation Number(s)	PL 04668/0237
Name and address of the authorisation holder	Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark

### III SCIENTIFIC OVERVIEW AND DISCUSSION

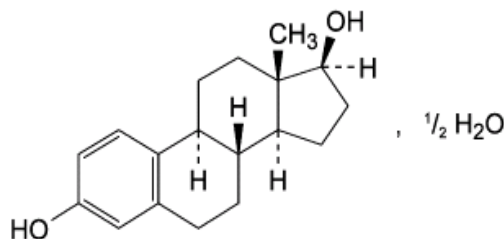
#### III.1 QUALITY ASPECTS

##### DRUG SUBSTANCE

INN: Estradiol hemihydrate

Chemical Names: Estra-1,3,5(10)-triene-3,17 $\beta$ -diol hemihydrate

Structure:



Molecular formula: C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>·1/2H<sub>2</sub>O

Molecular weight: 281.4

Physical form: A white crystalline powder

Estradiol hemihydrate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are controlled by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

Appropriate stability data have been generated, from studies carried out in accordance with ICH conditions. A suitable retest period has been set, based on the stability data provided.

##### DRUG PRODUCT

###### Other ingredients

Other ingredients consist of pharmaceutical excipients hypromellose, lactose monohydrate, maize starch, magnesium stearate and macrogol 6000. All excipients are controlled to their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients. With the exception of lactose monohydrate, none of the excipients used are sourced from materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the lactose is sourced from healthy animals under the same conditions as milk for human consumption.

###### Pharmaceutical Development

Suitable pharmaceutical development data have been provided for this application.

###### Manufacture

A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results appear satisfactory.

###### Finished product specification

The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**

Each tablet is contained in a disposable, single-use polyethylene/polypropylene applicator. Each applicator is packed separately in polyvinylchloride/aluminium foil blisters in pack sizes of 18 and 24 tablets.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidelines concerning materials in contact with food.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 3 years has been set with the storage conditions "Do not refrigerate".

**Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labelling**

The SPC, PIL and labelling are pharmaceutically satisfactory.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**MAA Form**

The MAA form is pharmaceutically satisfactory.

**Expert Report**

The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**

It is recommended that a Marketing Authorisation is granted for this application.

**III.2 PRE-CLINICAL ASPECTS****PHARMACODYNAMICS, PHARMACOKINETICS, TOXICOLOGY**

The pharmacodynamic, pharmacokinetic and toxicological properties of estradiol are well-known. Therefore, no further studies are required and the applicant provides none. An overview based on a literature review is, thus, appropriate. Additionally, the results of a study on vaginal tolerance in rabbits have been submitted. The reactions seen clinically at autopsy and by microscopic examination were induced mechanically, and thus no reaction was ascribed to the tablets.

**ENVIRONMENTAL RISK ASSESSMENT (ERA)**

Since estradiol acts as an endocrine disruptor once released in the environment, the applicant has committed to conducting a stepwise phase II ERA as a post approval follow-up measure, with an estimated deadline for completion by the first quarter of 2011.

**SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

The SPC is satisfactory from a preclinical viewpoint.

## NON-CLINICAL EXPERT REPORT

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

### OVERALL CONCLUSION ON THE NON-CLINICAL PART

The applicant has provided an adequate review of the available non-clinical data. There are no objections to the grant of a licence from a non-clinical point of view.

### III.3 CLINICAL ASPECTS

#### *Introduction*

The pharmacokinetics and pharmacodynamics of estradiol, the active ingredient of Vagifem 10 microgram Tablets, have been previously established in a previous submission for Vagifem 25 microgram Tablets.

Clinical documentation of this submission consists of three new studies. One clinical trial was conducted to demonstrate reduced systemic exposure of estradiol from the new formulation (the bioavailability study VAG-1850). The second study was designed to demonstrate efficacy and safety of the Vagifem 10 microgram formulation for the treatment of vaginal atrophy (study VAG-2195). The third study was designed to investigate the endometrial safety of Vagifem 10 microgram 17 beta-estradiol vaginal tablet in postmenopausal women with atrophic vaginitis symptoms.

In addition, during the clinical development of Vagifem 25 microgram, a lower 10 microgram strength was included as a comparator in three clinical trials. These studies have been assessed during the authorisation of Vagifem 25 microgram tablets.

**Study VAG-1850** was a pharmacokinetic study with a parallel group design to assess the extent of systemic absorption of estradiol during treatment with 10 microgram or 25 microgram estradiol vaginal tablet, administered once daily for 2 weeks, followed by 10 weeks of twice-weekly maintenance therapy, in postmenopausal women with atrophic vaginitis.

It was demonstrated that during administration in a regimen of repeated doses, the Vagifem 10 microgram tablet has a pharmacokinetic profile of key estrogen components similar to that of the currently-marketed Vagifem 25 microgram tablet. However, mean plasma concentrations of the estradiol, estrone, and estrone sulfate were consistently lower for the Vagifem 10 microgram tablet than the currently-marketed Vagifem 25 microgram formulation, indicating reduced systemic exposure to absorbed estradiol.

Normal plasma levels of estradiol in postmenopausal women fall within the range of 5-25pg/mL. For the purposes of the clinical trial VAG-1850, a plasma concentration of estradiol of 20pg/mL was selected as being a threshold of interest for measuring systemic absorption. As a result, estradiol levels below 20 pg/mL will definitely fall within the normal range of postmenopausal plasma concentrations and would, therefore, not be expected to produce any clinically relevant systemic effects.

Vagifem 10µg formulation had plasma estradiol concentrations (as measured by  $C_{ave(0-24)}$ ) below 20 pg/mL at all assessment days. Although more than 50% of the Vagifem 25µg tablet group had plasma estradiol  $C_{ave(0-24)}$  levels of  $\geq 20$  pg/mL at Day 1, by Day 14 this proportion was 37% and further declined to 15% after 10 weeks of maintenance therapy (Day 83). Mean estradiol  $C_{ave(0-24)}$  remained within the normal postmenopausal range on all assessment days for the Vagifem 25 microgram treatment group.

These results confirm that the Vagifem 10 microgram tablet is associated with lower systemic estrogen exposure as compared to the currently-marketed Vagifem 25 microgram tablet.

**Study VAG-2195** was a double-blind, randomized, multi-center, placebo-controlled, parallel-group trial conducted to evaluate the safety and efficacy of Vagifem 10 microgram compared to placebo during a 52-week study period.

The efficacy of Vagifem 10 microgram compared with placebo was demonstrated. Four co-primary endpoints were used without any corrections for multiple comparisons. Since statistical significance compared with placebo was demonstrated for all endpoints, no correction is needed. From the clinical point of view, the most important endpoint is an improvement in the most bothersome symptom. 95%CI for the most bothersome symptom did not include 'zero' indicating that Vagifem 10 microgram was better than placebo after 12 weeks' treatment. The treatment effect was maintained after 1 year.

Safety data with regard to the potential systemic effects of vaginally applied estrogen products have been very limited. In Study VAG-2195, gynecological and breast examination, PAP smear test, transvaginal ultrasound and endometrial biopsy were performed in approximately 160 women treated with 10 microgram of estrogen for 50 weeks. No additional safety concerns were revealed. Side effects reported are well-known side effects of estrogen therapy and vaginal administration.

Together with the pharmacokinetic data, it could be concluded that the systemic effects of Vagifem 10 microgram are negligible and no systemic progestagens are needed.

As a response to the Member States questions, the applicant submitted additional data to further support the endometrial safety of the Vagifem 10 microgram.

**Study VAG-1748** was a 12-month open-label multicentre trial to investigate the endometrial safety of Vagifem 10 microgram 17beta-estradiol vaginal tablet in postmenopausal women with atrophic vaginitis symptoms.

Eligible subjects were postmenopausal women aged 45 years or older at the time of screening, were postmenopausal  $\geq 2$  years after last menstruation (or bilateral oophorectomy performed 2 years or more prior to the time of screening), had serum follicle stimulating hormone (FSH) levels  $>40$  mIU/mL and estradiol  $<20$  pg/mL, and each subject had at least one urogenital symptom of moderate to severe intensity as identified by the subject (vaginal dryness, vaginal and/or vulvar irritation/itching, vaginal soreness, dysuria, dyspareunia and vaginal bleeding associated with sexual activity) during the week prior to screening period. Endometrial thickness  $<4.0$  mm (double layer), as measured by transvaginal ultrasound, was also required as an inclusion criterion.

Using the supplied applicator, each enrolled patient inserted one Vagifem 10 microgram vaginal tablet once daily during the first 2 weeks of treatment. Subjects then inserted the tablets twice weekly during the remainder of the trial (maintenance treatment duration was 50 weeks).

Endometrial biopsies were taken at baseline and after 52 weeks of treatment. Among women withdrawn from the study, only subjects treated for 3 months or longer were to have an "end of treatment" biopsy. Endometrial biopsy, as well as transvaginal ultrasounds, was used for

evaluation of the endometrium. Transvaginal ultrasound examination preceded all endometrial biopsies.

The total number of subjects who received end-of-treatment endometrial biopsies (including premature discontinuation) was 297. The number of completers who had biopsy results at Week 52 was 283.

Of the 283 completers, 261 had interpretable results for the evaluation of hyperplasia rate at Week 52 according to protocol definitions “no tissue” results were not to be included in the evaluation of the hyperplasia rate.

For the evaluation of endometrial safety, endometrial biopsy results from the studies VAG-2195 (efficacy study) and VAG-1748 (safety study) were pooled. The total number of subjects exposed to Vagifem 10 microgram in the combined study population was 541. Of these, 453 (83.7%) out of 541 subjects in the Vagifem 10 microgram group completed at least 49 weeks of study.

The total number of analysable biopsy at 12 months was 386 for the combined Vagifem 10µg group. Two cases of endometrial hyperplasia/carcinoma were identified in the pooled Vagifem 10 microgram population of 386 subjects. The incidence rate of hyperplasia/carcinoma was 0.52% for the combined Vagifem 10 microgram treatment group. The one-sided 95% confidence interval for the Vagifem 10 microgram treatment group was [0, 1.6%], and the two-sided 95% confidence interval was [0.06%, 1.86%]. The upper bound of the two-sided 95% confidence interval was below the required 2% stated in *Guideline on Clinical Investigation of Medicinal Products for Hormone Replacement Therapy of Oestrogen Deficiency Symptoms in Postmenopausal Women* (EMA/CHMP/021/97/Rev1). Therefore, requirements from the EMA are met and endometrial safety has been demonstrated.

*Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and labelling*  
The SPC, PIL and labelling are medically satisfactory.

#### *Clinical Expert Report*

The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

#### *MAA Form*

The MAA Form is medically satisfactory.

#### *Clinical Conclusion*

The grant of a Marketing Authorisation is recommended.

#### **IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY**

The important quality characteristics of Vagifem 10 microgram Vaginal Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

#### **PRECLINICAL**

The preclinical data submitted have not revealed any evidence of potential risks to human health from treatment with Vagifem 10 microgram Vaginal Tablets beyond those already described.

#### **EFFICACY**

Three new studies were submitted: one pharmacokinetic study comparing estradiol levels in the 10 and 25 microgram formulations; one efficacy study comparing 52 weeks for 10 microgram product versus placebo; one safety study investigating the endometrial safety of the product.

The pharmacokinetic study showed that Vagifem 10 microgram tablets are associated with lower systemic estrogen exposure as compared to the currently-marketed Vagifem 25 microgram tablet.

The efficacy study showed that the 10 microgram formulation was better than placebo at improving “the most bothersome symptom” in women treated for 12 weeks, which was maintained after 1 year. No additional safety concerns were revealed. Side effects reported are well-known side effects of estrogen therapy and vaginal administration.

The safety study results were compared in a meta-analysis with the efficacy study discussed above. The incidence rate of hyperplasia and/or carcinoma was within limits stated in the *Guideline on Clinical Investigation of Medicinal Products for Hormone Replacement Therapy of Oestrogen Deficiency Symptoms in Postmenopausal Women* (EMA/CHMP/021/97/Rev1), indicating that there is no increased risk in this patient group.

The SPC, PIL and labelling are satisfactory.

#### **BENEFIT-RISK ASSESSMENT**

The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s product and the innovator product are interchangeable. Extensive clinical experience with estradiol hemihydrate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome