

## 6 Summary of activities in the risk management plan by product

### 6.1 Elements for summary tables in the EPAR

#### 6.1.1 Summary table of safety concerns

The important identified and potential risks for Vagifem® 10 µg are summarised in [Table 6–1](#).

**Table 6–1 Summary table of safety concerns**

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"><li>• Oestrogen-dependent malignancies (breast cancer, endometrial cancer, ovarian cancer)</li><li>• Venous thromboembolism (deep vein thrombosis, pulmonary embolism)</li><li>• Coronary artery disease</li><li>• Ischaemic stroke</li></ul>
Important potential risks	<ul style="list-style-type: none"><li>• Allergic reactions</li></ul>
Missing information	None

#### 6.1.2 Table of ongoing and planned additional pharmacovigilance studies/activities in the pharmacovigilance plan

There are no planned or ongoing additional pharmacovigilance activities for Vagifem® 10 µg that are imposed, mandatory or required.

#### 6.1.3 Summary of post-authorisation efficacy development plan

No post-authorisation efficacy studies for Vagifem® 10 µg have been performed or planned.

#### 6.1.4 Summary table of risk minimisation measures

The risk minimisation measures for the important identified and potential risks for Vagifem® 10 µg are summarised in [Table 6–2](#).

**Table 6–2 Summary table of risk minimisation measures**

<b>Safety concern</b>	<b>Routine risk minimisation measures SmPC Text</b>	<b>Additional risk minimisation measures</b>
Oestrogen-dependent malignancies (breast cancer, endometrial cancer, ovarian cancer)	Current text mentioned in Section 4.3 ‘Contraindications’, Section 4.4 ‘Special warnings and precautions for use’ and Section 4.8 ‘Undesirable effects’ in SmPC is considered adequate.	None
Venous thromboembolism (deep vein thrombosis, pulmonary embolism)	Current text mentioned in Section 4.3 ‘Contraindications’, Section 4.4 ‘Special warnings and precautions for use’ and Section 4.8 ‘Undesirable effects’ in SmPC is considered adequate.	None
Coronary artery disease	Current text mentioned in Section 4.3 ‘Contraindication’, Section 4.4 ‘Special warnings and precautions for use’ and Section 4.8 ‘Undesirable effects’ in SmPC is considered adequate.	None
Ischaemic stroke	Current text mentioned in Section 4.4 ‘Special warnings and precautions for use’ and Section 4.8 ‘Undesirable effects’ in SmPC is considered adequate.	None
Allergic reactions	Current text mentioned in Section 4.2 ‘Contraindications’ in SmPC is considered adequate.	None

**Abbreviations:** SmPC = Summary of Product Characteristics.

## **6.2 Elements for a public summary**

### **6.2.1 Overview of disease epidemiology**

#### **What is vaginal atrophy?**

Postmenopause is a period in a woman's life after she had her last menstrual period. Vaginal atrophy is a condition in which postmenopausal women develop symptoms such as redness, itching, and dryness of the vagina, which may have a negative affect on their quality of life.

#### **What are the causes of vaginal atrophy?**

Oestrogen is the female sex hormone which is responsible for keeping the skin of the vagina healthy, more elastic and moist. When oestrogen levels decline at menopause, the skin of the vagina becomes thinner and less elastic, and the fluid secretions from the vagina also decrease. All these changes commonly lead to symptoms such as dryness, burning and itching at vagina, painful intercourse, and bleeding during and after intercourse.

#### **How common is vaginal atrophy?**

Vaginal atrophy occurs in the majority of women after menopause; however, only half of the women with the condition experience any related symptoms. In general, the risk of experiencing any symptoms increases with time.

### **6.2.2 Summary of treatment benefits**

#### **What is the current treatment for vaginal atrophy?**

Treatment options available for vaginal atrophy include use of vaginal lubricants and moisturisers for mild symptoms, or hormonal therapy for more troublesome symptoms.

Hormone therapy can be in the form of a tablet, gel, patch, vaginal tablet or creams. Vaginal tablet and creams provides oestrogen locally to vagina and surrounding tissues, without giving oestrogen to the whole body. The North American Menopause Society recommends that lowest effective dose of locally administered oestrogen should be the treatment of choice for treating vaginal atrophy symptoms.

#### **Where does Vagifem® 10 µg fit in?**

Vagifem® 10 µg is a vaginal tablet which is used to provide relief from the symptoms associated with vaginal atrophy. This product works by replacing the oestrogen which is normally produced by the ovaries of the women. It is inserted into the vagina with the help of the applicator.

## What studies have been done with Vagifem® 10 µg?

In total, 570 postmenopausal women with vaginal atrophy were treated with Vagifem® 10 µg in the three main clinical trials. The studies have shown that Vagifem® 10 µg provides sufficient oestrogen to relieve symptoms of vaginal atrophy and reverse the vaginal changes associated with menopause, with the added benefit of very small amount of medicine reaching the bloodstream.

### 6.2.3 Unknowns relating to treatment benefits

Vagifem® 10 µg and the higher dosed version (Vagifem® 25 µg) have been in the market for a long period of time. It has also been well studied for the approved indications. The efficacy and safety profile of Vagifem® 10 µg is well established and is in accordance with the product label.

### 6.2.4 Summary of safety concerns

The risks which are described below are based on the effects of the oestrogen (hormone) administered through the mouth. Vagifem® 10 µg is a product which is administered locally in the vagina and a very small amount of drug reaches the blood. Therefore, it is uncertain whether repeated use of local vaginally administered oestrogen products such as Vagifem® 10 µg possesses similar risks.

The summary of the important identified and potential risks is summarised in [Table 6–3](#) and [Table 6–4](#), respectively.

**Table 6–3 Summary of safety concerns – Important identified risks**

Risk	What is known	Preventability
<p>Cancers which are sensitive to oestrogen such as breast cancer, cancer of the womb lining (endometrium) and ovarian cancer</p> <p>(Oestrogen-dependent malignancies [breast cancer, endometrial cancer, ovarian cancer])</p>	<p>Postmenopausal women treated with hormonal therapy have an increased risk of developing some cancers, such as breast cancer, endometrial cancer, and ovarian cancer; this may be related to high levels of estradiol in blood.</p> <p>However, when considering all the results from the use of Vagifem® 10 µg in humans, there are no conclusive data establishing a risk of developing these cancers with local vaginal application of oestrogens.</p>	<p>Vagifem® 10 µg should not be used in women who had a history or possess the risk of developing breast or endometrial cancer.</p> <p>A doctor should be consulted immediately if there is any breakthrough vaginal bleeding.</p> <p>Regularly check your breasts and see a doctor if you notice any changes such as:</p> <ul style="list-style-type: none"> <li>• dimpling of the skin</li> <li>• changes in the nipple</li> <li>• any lumps you can see or feel.</li> </ul>

Risk	What is known	Preventability
<p>Blood clots in the vein, such as in the legs or the lungs</p> <p>(Venous thromboembolism [deep vein thrombosis, pulmonary embolism])</p>	<p>The risk of developing blood clots in veins increases after treatment with oral oestrogen therapy. These blood clots can be serious, and if one travels to the lungs, it can cause chest pain, breathlessness and fainting.</p> <p>There are no conclusive data establishing an increased risk of blood clots in veins with local vaginal application of oestrogens. Therefore, the possibility of developing a blood clot in the vein, such as in the legs (deep venous thrombosis) or the lungs (pulmonary embolism) is considered to be very low with Vagifem® 10 µg.</p>	<p>Vagifem® 10 µg should not be used in women who have or ever had a blood clot in the vein, such as in the legs (deep venous thrombosis) or the lungs (pulmonary embolism). It should also not be used in women who have a blood clotting disorder.</p> <p>A doctor should be consulted immediately if you notice signs of a blood clot, such as:</p> <ul style="list-style-type: none"> <li>• painful swelling and redness of the legs</li> <li>• sudden chest pain</li> <li>• difficulty in breathing.</li> </ul>
<p>Heart disease</p> <p>(Coronary artery disease)</p>	<p>Women over the age of 60 years who use hormonal treatment (oestrogen with another female hormone called progestagen) are slightly more likely to develop heart disease than those not taking any hormonal treatment.</p> <p>There are no conclusive data establishing a risk of heart disease with local vaginal application of oestrogens. Therefore, the possibility of developing a heart disease is considered to be very low with Vagifem® 10 µg.</p>	<p>Vagifem® 10 µg should not be used in women who have or have ever had a heart disease caused by blood clots in the arteries.</p> <p>A doctor should be consulted if there is a large rise in your blood pressure and you experience chest pain, abnormal heart beats, or significant tiredness.</p>
<p>Ischaemic stroke</p>	<p>The risk of getting a stroke is higher in women taking hormonal treatment than in those not taking any hormonal treatment. In addition, the number of extra cases of stroke due to use of hormonal treatment increases with age.</p> <p>There are no conclusive data establishing a risk of stroke with local vaginal application of oestrogens. Therefore, the possibility of developing a stroke is considered to be very low with Vagifem® 10 µg.</p>	<p>Vagifem® 10 µg should not be used in women who have or have ever had a stroke.</p> <p>A doctor should be consulted if you experience headache, dizziness, and tiredness.</p>

**Table 6–4 Summary of safety concerns – Important potential risks**

Risk	What is known (Including reason why it is considered a potential risk)
Allergic reactions	Vagifem® 10 µg can cause allergic reactions in some women if they are allergic to the active ingredient (estradiol) or any other excipients of this medicine. Do not use Vagifem® 10 µg if you are allergic to any of the ingredients of this medicine.

**Table 6–5 Summary of safety concerns – Missing information**

Risk	What is known
None	

**6.2.5 Summary of additional risk minimisation measures by safety concern**

There are no additional risk minimisation measures for any of the safety concerns.

**6.2.6 Planned post-authorisation development plan**

There are no planned post-authorisation safety or efficacy studies for Vagifem® 10 µg.

**6.2.7 Summary of changes to the risk management plan over time**

The changes to the risk management plan over time is summarised in [Table 6–6](#).

**Table 6–6 Major changes to the risk management plan over time**

<b>Version</b>	<b>Date</b>	<b>Safety concerns</b>	<b>Comment</b>
<b>Edition 1, Version 1</b>	27 Aug 2008	<p><b>Important Identified Risks</b>  Potential systemic class effects: breast cancer, endometrial cancer, cardiovascular disease, dementia)</p> <p><b>Important Potential Risks</b>  Allergic reactions</p> <p><b>Information Missing Information</b>  Safety/AE experience in population not covered in the Vagifem® 10 µg development programme long term safety and efficacy data</p>	None
<b>Edition 2, Version 1</b>	17 May2010	No change in the safety concern.	Section on clinical trial exposure was updated.
<b>Edition 3, Version 1</b>	07 Mar 2014	<p>The risk of ‘Dementia’ has been re-classified from important identified risk to identified risk not categorised as important.</p> <p>In addition, no important information regarding the safety of Vagifem® 10 µg in the population of postmenopausal women not studied in clinical trials is considered missing. Therefore, there is no missing information for Vagifem® 10 µg.</p>	The RMP has been updated in accordance with the new guidance on format of the risk management plan. Furthermore, terminology and wording have been aligned throughout the document to ensure consistency.

**Abbreviations:** AE = adverse event; RMP = risk management plan.