Femoston 1/10 film-coated tablet
Femoston 2/10 film-coated tablet
Femoston Conti 1/5 film-coated tablet
Femoston Conti 0.5/2.5 film-coated tablet

19 Feb 2014, Version 1.0

SUMMARY OF RISKMANAGEMENT PLAN

VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Menopause starts when a woman's ovaries stop producing egg cells and the amount of estrogen produced by a woman's body decreases. The most obvious sign of menopause is when the menstrual bleeding cycle stops (amenorrhea). A woman is said to be postmenopausal when she has not had menstrual bleeding for at least 12 months. This usually occurs between 45 and 55 years of age. Many postmenopausal women experience symptoms such as hot flushes, night sweats, sleep problems, vaginal dryness or problems with mood such as sadness or difficulty concentrating. These symptoms usually last for several years and may seriously hinder daily life of some women. In some women, the lack of estrogen after the menopause may also cause the bones to become abnormally fragile and easily fractured.

VI.2.2 Summary of Treatment Benefits

Estradiol/dydrogesterone contains the female hormone estradiol. Estradiol is given to replace the estrogen that is not produced anymore by a woman's body after menopause, thereby relieving the symptoms of menopause. This is called hormone replacement therapy (HRT). The treatment benefits of the different formulations of estradiol/dydrogesterone were examined in a series of studies where the drug was given to almost 5,000 postmenopausal women. These studies showed that estradiol/dydrogesterone relieves some of the symptoms of menopause (such as hot flushes, night sweats, sweating attacks and sleeping difficulties) and improves the quality of life (as measured in questionnaires completed by the women participating in these studies). Only few patients (1-2%) prematurely discontinued estradiol/dydrogesterone study treatment because they felt that the treatment did not improve their symptoms. Studies in postmenopausal women have also shown that estradiol/dydrogesterone increases bone mineral density.

In postmenopausal women with an intact womb, taking estrogen-only HRT can cause excessive thickening of the lining of the womb (this is called "endometrial hyperplasia") and increase the risk for cancer of the womb lining (this is called "endometrial cancer"). To protect patients from these risks, estradiol/dydrogesterone also contains dydrogesterone. Dydrogesterone is a synthetic hormone that acts like the natural hormone progesterone and opposes the unfavorable effects of estrogens on the lining of the womb.

VI.2.3 Unknowns Relating to Treatment Benefits

The women who participated in the studies with estradiol/dydrogesterone were mostly white and younger than 65 years. Therefore, information on treatment benefits in older women and women with a different ethnic background is limited. However, estradiol/dydrogesterone has been prescribed to patients since 1995, and experience with the marketed product has amounted to more than five million patient-years. To date, there has been no indication that estradiol/dydrogesterone might not work in certain people.

VI.2.4 Summary of Safety Concerns

Table 30. Important Identified Risks

Risk	What Is Known	Preventability
Blood clots in an artery of the heart; heart attack (Coronary heart disease)	Studies with other HRT products have shown that heart attacks occur more often in women over the age of 70 using HRT compared to women of the same age not using HRT. There is probably no increased risk of heart attacks related to HRT in women who started HRT within 10 years of becoming menopausal or are younger than 60 years old.	No method for predicting or preventing a heart attack in an individual women taking HRT is known. Women who have or recently have had a disease caused by blood clots in the arteries, such as a heart attack, stroke or angina should not take estradiol/dydrogesterone.
Stroke	Studies with other HRT products have shown that risk of having a stroke is about 1.3 times higher in HRT users than in non-users. It has been estimated that during five years of HRT, there are approximately one and three additional strokes per 1,000 HRT users aged 50-59, and 60-69, respectively.	No method for predicting or preventing a stroke in an individual women taking HRT is known. Women who have or recently have had a disease caused by blood clots in the arteries, such as a heart attack, stroke or angina should not take estradiol/dydrogesterone.
Blood clots in a vein (venous thrombo-embolism)	Studies with other HRT products have shown that risk of developing a blood clot in a vein (deep vein thrombosis) or in the lungs (pulmonary embolism) is approximately doubled in HRT users as compared to non-users. It has been estimated that during five years of HRT, there are approximately five and 10 additional venous blood clots per 1,000 HRT users aged 50-59, and 60-69, respectively.	No method for predicting or preventing a venous blood clot in an individual women taking HRT is known. Women who have or recently have had a venous blood clot or are aware of a family history of a blood clotting disorder should not take estradiol/dydrogesterone.

Table 30. Important Identified Risks		
Risk	**What Is Known**	**Preventability**
Breast cancer	Among women aged 50-79 who are not taking HRT, on average, nine to 17 in 1,000 will be diagnosed with breast cancer over a 5-year period. Studies with other HRT products have shown that for women aged 50-79 who are taking HRT over five years, there will be an extra four to six cases in 1,000 users. Breast cancer risk returns to normal within a few years after stopping treatment.	No method for predicting or preventing the occurrence of breast cancer in an individual women taking HRT is known. Women with known or suspected breast cancer should not take estradiol/dydrogesterone. Women using HRT should regularly check their breast for any changes.
Cancer of the ovaries (ovarian cancer)	Studies with other HRT products have shown a small increase in the risk of developing ovarian cancer in HRT users as compared to non-users. Because ovarian cancer is a rare disease, it is estimated that during five years of HRT, there is less than one additional case of ovarian cancer per 1,000 HRT users.	No method for predicting or preventing the occurrence of ovarian cancer in an individual women taking HRT is known.
Cancer of the lining of the womb (endometrial cancer)	Studies with estrogen-only HRT products in women with an intact womb have shown that taking estrogen- only HRT will increase the risk of excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the womb lining (endometrial cancer). The dydrogesterone in estradiol/dydrogesterone probably completely eliminates this extra risk.	No method for predicting or preventing the occurrence of endometrial cancer in an individual women taking HRT is known. Women with known or suspected endometrial cancer, unexplained vaginal bleeding, or excessive thickening of the womb lining (endometrial hyperplasia) that is not being treated, should not take estradiol/dydrogesterone. Women using HRT should see their doctor if their bleeding pattern differs from what is normal during treatment with estradiol/dydrogesterone (see Package Leaflet for details).

Table 30. Important Identified Risks		
Risk	**What Is Known**	**Preventability**
Liver disorders	Based on isolated case reports and experience with other hormone therapies (such as oral contraception), it cannot be excluded that HRT causes certain liver disorders, such as benign liver tumors, to occur or worsen.	No method for predicting or preventing the occurrence of a liver disorder in an individual women taking HRT is known. Women should not take estradiol/dydrogesterone if they have a liver disease or have ever had a liver disease, unless their liver function tests have returned to normal.
Gallbladder disorders	Studies with other HRT products have shown an increased risk of developing gallbladder disease such as gallstones, or requiring surgical removal of the gallbladder due to gallstones in HRT users as compared to non-users. It has been estimated that there are approximately 20 additional cases of gallstones, gallbladder inflammation, or gallbladder removal per 10,000 person-years of HRT use.	No method for predicting or preventing the occurrence of a gallbladder disorder in an individual women taking HRT is known.

Table 31. Important Potential Risks	
Risk	**What is Known (Including Reason Why It Is Considered a Potential risk)**
None	N/A

Table 32. Missing Information	
Risk	**What Is Known**
None	N/A

VI.2.5 Summary of Risk Minimization Measures by Safety Concern

All medicines have a Summary of Product Characteristics which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided for patients in the form of the Package Leaflet. The measures described in these documents are known as routine risk minimization measures. The Summary of Product Characteristics and the Package Leaflet for estradiol/dydrogesterone can be found in the European Public Assessment Report on estradiol/dydrogesterone. This medicine has no additional risk minimization measures.

VI.2.6 Planned Post-Authorization Development Plan

No post-authorization studies relating to safety concern or efficacy issue are currently ongoing or planned.

VI.2.7 Summary of Changes to the Risk Management Plan over Time

The major changes to the risk management plan over time is detailed in table below.

Table 33. List of Major Changes to the Risk Management Plan

Version	Date	Safety Concerns	Comment
1.0	19 FEB 2014	• Coronary heart disease • Stroke • Venous thromboembolism • Breast cancer • Ovarian cancer • Endometrial cancer • Hepatic disorders • Gallbladder disorders	This RMP was issued to support a new marketing authorization application. Preparation of this RMP was not triggered by a newly identified safety concern or new information relating to a known safety concern.