Part VI.2 Elements for a Public Summary

Part VI.2.1 Overview of disease epidemiology

In the perimenopause, hormonal changes take place and symptoms might appear which deteriorate the quality of life, like hot flushes, night sweats, sleep problems, hair loss, weight gain and mood changes. Moreover, there are metabolic changes (processes in the body), which cause a decrease in bone mass.

Osteoporosis causes a decrease in the amount of calcium in the bone and the bone becomes weaker. More females have osteoporosis than males, especially after menopause. In Europe, approximately 30% of all women after menopause (cessation of a woman's ability to give rise to offspring) have osteoporosis and at least 40% of these women will sustain one or more fractures during their lifetime (Melton, Chrischilles, Cooper, Lane, & Riggs, 1992). Due to worldwide ageing populations a notable increase in the frequency of osteoporosis in women after menopause is likely. The frequency of osteoporosis rises from 5% among women aged 50 years to 50% at 85 years of age. Among men, the comparable numbers are 2.4% and 20%, respectively (Woolf & Pfleger, 2003). The highest frequency of osteoporosis in Europe is seen in the Scandinavian countries, in particular Norway, where more than 100 of 10,000 people have hip fractures (Lofthus et al., 2001).

Part VI.2.2 Summary of treatment benefits

Estrogen deficiency at menopause is associated with a decline in bone mass. The effect of estrogens on the bone mineral density is dose-dependent. Protection appears to be effective for as long as treatment is continued. After discontinuation of Hormone Replacement Therapy (HRT), bone mass is lost at a rate similar to that in untreated women. Evidence from the Women's Health Initiative (WHI) trial and meta-analyzed trials shows that current use of HRT, alone or in combination with a progestagen – given to predominantly healthy women – reduces the risk of hip, vertebral, and other osteoporotic fractures. HRT may also prevent fractures in women with low bone density and/or established osteoporosis, but the evidence for that is limited (SUMMARY OF PRODUCT CHARACTERISTICS). Several trials showed that compared to placebo, a rapid, statistically significant decrease in the frequency and severity of hot flushes could be achieved which continued throughout the study, with good safety profiles (Panay, Ylikorkala, Archer, Gut, & Lang, 2007). HRT treatments also induced a significant improvement in the quality-of-life assessments (Pornel & Spielmann, 2005).

Part VI.2.3 Unknowns relating to treatment benefits

There are no adequate data on the use of Estradiol+ Norethisterone acetate 1 mg + 500 mcg, film-coated tablet in women older than 65 years.

Part VI.2.4 Summary of safety concerns

Table 7-1 Important identified risks

Risk	What is known	Preventability
Embolic and thrombotic events (including cardiovascular disease and stroke)	The risk of blood clots in the veins is about 1.3 to 3- times higher in Hormone Replacement Therapy (HRT) users than in non-users, especially during the first year of taking it.	Estradiol+ Norethisterone acetate 1 mg + 500 mcg, film-coated tablet should not be used in the presence of embolic and thrombotic events present or in history (deep venous

Risk	What is known	Preventability
	Blood clots can be serious, and if one travels to the lungs, it can cause chest pain, breathlessness, fainting or even death. There is no evidence that HRT will prevent a heart attack. Women over the age of 60 years who use estrogen-progestogen HRT are slightly more likely to develop heart disease than those not taking any HRT. The risk of getting stroke is about 1.5 times higher in HRT users than in non-users. The number of extra cases of stroke due to use of HRT will increase with age.	thrombosis, pulmonary embolism). Should an embolic or thrombotic event appear for the first time during Estradiol+ Norethisterone acetate use, the product should be stopped.
Increase in blood pressure	Increase in blood pressure has been reported by users of HRT.	In cases of increases in blood pressure, Estradiol+ Norethisterone acetate 1 mg + 500 mcg, film-coated tablet should be discontinued. This also applies if during the use of Estradiol+ Norethisterone acetate in preexisting high blood pressure, constantly elevated blood pressure values or a remarkable increase in blood pressure do not respond to treatment against it.
Abnormal liver function	Acute or chronic disturbances of liver function may occur during HRT use.	Prior to starting of Estradiol+ Norethisterone acetate 1 mg + 500 mcg, film-coated tablet, a complete medical history (including family history) should be taken and a physical examination should be performed, guided by the contraindications and warnings. Presence or history of severe liver disease as long as liver function values have not returned to normal is a contraindication for Estradiol+ Norethisterone acetate.
Breast cancer	Taking combined estrogen-progestogen and possibly also estrogen-only HRT increases the risk of breast cancer. The extra risk depends on how long you take HRT. The additional risk becomes clear within a few	Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and

Risk	What is known	Preventability
	years. However, it returns to normal within a few years (at most 5) after stopping treatment.	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.
Endometrial hyperplasia and carcinoma	Excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the womb lining (endometrial cancer) are reported in women taking estrogens alone for prolonged periods.	Combined estrogen-progestagen therapy like Estradiol+ Norethisterone acetate in non-hysterectomized women prevents the excess risk associated with estrogen-only HRT.

Table 7-2 Important potential risks

Risk	What is known
Ovarian cancer	Ovarian cancer is rare - much rarer than breast cancer. The use of estrogen-only or combined estrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer. The risk of ovarian cancer varies with age. For example, in women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period. For women who have been taking HRT for 5 years, there will be about 3 cases per 2000 users (i.e. about 1 extra case).
Pancreatitis (in patients with hypertriglyceridemia)	Women with pre-existing hypertriglyceridemia should be followed closely during estrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition.

Table 7-3 Missing information

None

Part VI.2.5 Summary of additional risk minimization measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) 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 in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

This medicine has no additional risk minimization measures.

Part VI.2.6 Planned post authorization development plan

None

Part VI.2.7 Summary of changes to the Risk Management Plan over time

Table 7-8 Major Changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
2.0	26 Aug 2016	Ovarian Cancer	According to RMS Day 70 PrAR dated 24 May 2016 in CZ/H/0678/001/DC updated wording from updated SmPC (in line with PRAC recommendation from 03 Dec 2015) added concerning ovarian cancer (Part V.1, VI.2.4).
		N/A	Part II Module SV, Annex 2 and 3 updated