VI.2 Elements for a public summary

VI.2.1 Overview of Disease Epidemiology

The menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity, and it marks the end of a woman's reproductive capacity. It is a retrospective diagnosis usually made after 12 months of amenorrhoea, and may be genetically determined. Symptoms often begin in the perimenopausal years. In the UK, the mean age for the menopause is 50 years and 9 months. This has changed very little over the last 100 years despite a fall in the average age of menarche. Apart from radiation, cytotoxic drugs and smoking, very little affects the onset of ovarian failure. The median onset of the perimenopause is between 45.5 and 47.5 years, and it lasts for an average of 4 years. The menopausal transition refers to the time of the perimenopause prior to the last menstrual period, and is a transition phase from fertile ovulatory cycles with well-characterized hormonal profiles to the postmenopause with low oestrogen and progesterone and high gonadotrophin levels (Bruce D, et al. 2009). One of the major concerns after menopause is the development of osteoporosis. Osteoporosis-related fractures affect one-third of postmenopausal women, resulting in significant morbidity, mortality and cost (De Villiers TJ 2009).

VI.2.2. Summary of treatment benefits

The MAA is literature based. Consequently any clinical efficacy studies have been performed by the MAH. For details please refer to sections Module 2.5 and Module 2.7 of the current version of the MA dossier.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Risk	**What is known?**	**Preventability**
1. Important identified risks		
Stroke	In a large study, it was found that women treated with tibolone had a higher risk of stroke relative to placebo. But only in women with 70 years and over the real risk was increased.	To prevent such events, contraindications must be taken into account. Appropriate check-ups should be held regularly. Contraindication: Any history of arterial thromboembolic disease Measures:

Risk	What is known?	Preventability
		Regular therapy monitoring
Breast cancer	The British Million Women Study involved a cohort of postmenopausal aged 50 to 64 years who were monitored for an average of 2.6 years. Among the women who used hormone replacement therapy, 6% took tibolone. Among the women treated with tibolone, the risk of being diagnosed with invasive breast cancer was higher than in women who did not use hormone replacement therapy. In detail, the incidence of breast cancer was found significantly increased for current users of preparations containing tibolone.	To prevent such events, contraindications and warnings must be taken into account. Appropriate check-ups should be held regularly. Contraindication: Known, past or suspected breast cancer Precautions: 1st grade relatives with a history of breast cancer Measures: Regular therapy control, including mammography
Cancer of the endometrium (Endometrial cancer)	The available information is not clear. In general, it is accepted, that tibolone does not stimulate significantly the endometrial. Nevertheless, 31 cases of endometrial cancer per 10,000 women using tibolone for more than three years. Other study data did not confirm this observation. In general, the development of endometrial cancer associated to preferentially prolonged use of tibolone cannot be fully excluded.	To prevent such events, contraindications must be taken into account. Appropriate check-ups should be held regularly. Contraindication: known, past or suspected endometrial cancer Measures: Regular therapy control
2. Important potential risks		
Coronary heart disease/heart attack (Coronary artery disease/Myocardial infarction)	The role of hormone replacement therapy for coronary risk is widely discussed. The available information for tibolone is contradictory. In a large epidemiological study the group of tibolone users was to small to detect differences with non-users. The only clear statement resulting from this study was that tibolone does not protect against myocardial infarction. The contradictory database and the detected very small differences in risk assessment did not allow classifying the risk as identified risk. Nevertheless, a risk cannot be fully excluded.	
Vein thrombosis, pulmonary embolism (Venous	It was considered that the results of the GPRD study indicated no increased risk of venous thromboembolism during short-term use of tibolone. However,	

Risk	What is known?	Preventability
thromboembolism)	the data are too limited to conclude that an increased risk during tibolone use compared with non-use can be excluded.	
Ovarian cancer	The risk of ovarian cancer is discussed using data from Million Women study, indicating that tibolone use may have the same relative risk for ovarian cancer than other HRTs. On the other hand, the 5-year risk of ovarian cancer in women taking HRTs is small and lower than that associated with obesity, lack of physical exercise, smoking, and nulliparity. Regarding this database, a risk cannot be fully excluded, but the data did not allow classifying other than potential risk.	
3. Important missing information		
	None.	

VI.2.5 Summary of additional risk minimisation measures by safety concern

The summary of product characteristics and the package leaflet will contain suitable and clear information concerning the potential risks.

The risk management plan will be started with routine pharmacovigilance activities and specified if necessary.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Not applicable at present.