PART VI SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Summary of risk management plan for tibolone

This is a summary of the risk management plan (RMP) for tibolone. The RMP details important risks of tibolone, how these risks can be minimised, and how more information will be obtained about tibolone's risks and uncertainties (missing information).

Tibolone's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how tibolone should be used.

I. The medicine and what it is used for

Tibolone is authorised for relief of symptoms occurring after menopause and prevention of osteoporosis (see SmPC for the full indication). It contains tibolone as the active substance and it is given by mouth.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of tibolone, together with measures to minimise such risks and the proposed studies for learning more about tibolone's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of tibolone are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of tibolone. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this

association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table II.A.1 List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Endometrial Cancer Breast Cancer Stroke
Important potential risks	Myocardial Infarction Ovarian Cancer Venous thromboembolic events
Missing information	None

II.B Summary of Important Risks

Table II.B.1 Important Identified Risk – Endometrial Cancer

Evidence for linking the risk to the medicine	MWS, GPRD.
Risk factors and risk groups	Risk factors: increasing age, long-term exposure to ET (endogenous (e.g., anovulation, PCOS) and exogenous), metabolic syndrome (obesity, diabetes), nulliparity. Any irregular/unscheduled vaginal bleeding, for which there is no obvious cause, should be investigated before starting tibolone and during treatment.
Risk minimisation measures	Routine risk minimisation measures

Table II.B.2 Important Identified Risk – Breast Cancer

Evidence for linking the risk to the medicine	Observational studies (MWS, GPRD)
Risk factors and risk groups	Risk factors: age, obesity, history of breast cancer, 1st degree heredity for breast cancer, genetic risk factors
Risk minimisation measures	Routine risk minimisation measures

Table II.B.3 Important Identified Risk – Stroke (ischaemic and haemorrhagic cerebrovascular conditions)

Evidence for linking the risk to the medicine	Observational studies (MWS and GPRD)
Risk factors and risk groups	Risk factors: age, family history, obesity, diabetes, hypertension, smoking, atrial fibrillation, history of transient ischaemic attack
Risk minimisation measures	Routine risk minimisation measures

Table II.B.4 Important Potential Risk – Myocardial infarction

Evidence for linking the risk to the medicine	Clinical and observational studies
Risk factors and risk groups	Risk factors: age, obesity, diabetes, hypertension, smoking, alcohol, hypercholesterolemia, family history of MI (hereditary)
Risk minimisation measures	Routine risk minimisation measures

Table II.B.5 Important Potential Risk – Ovarian Cancer

Evidence for linking the risk to the medicine	Collaborative Group on Epidemiological Studies of Ovarian Cancer 2015[Ref. 5.4: 04LDXC] ; Clinical Overview INT00098314 march 2009
Risk factors and risk groups	Risk factors for ovarian cancer include increasing age, nulligravidity, infertility, endometriosis, late menopause and hereditary ovarian cancer syndromes (*BRCA* gene mutations, Lynch syndrome). [Ref. 5.4: 04TW8J]
Risk minimisation measures	Routine risk minimisation measures

Table II.B.6 Important Potential Risk – Venous Thromboembolic Events

Evidence for linking the risk to the medicine	Clinical and Observational studies (MWS and GPRD)
Risk factors and risk groups	Risk Factors: older age, major surgery, prolonged immobilization obesity (BMI > 30 kg/m2), pregnancy and postpartum period (not applicable to tibolone which is for use in menopausal women), systemic lupus erythematosus (SLE) and cancer. There is no consensus about the possible role of varicose veins in VTE.
Risk minimisation measures	Routine risk minimisation measures

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of tibolone.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for tibolone.