SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

LIVIFEM® Tablets

COMPOSITION

Each tablet contains 2,5 mg tibolone.

LIVIFEM tablets contain potato starch, magnesium stearate, ascorbyl palmitate and lactose.

Contains lactose.

PHARMACOLOGICAL CLASSIFICATION

A.21.13 Others

Pharmacological action

LIVIFEM stabilises the hypothalamic-pituitary system after failure of the ovarian function in the climacteric, which leads to the occurrence of vasomotor complaints as a result of the involvement of the thermoregulatory centre in the hypothalamus. The therapeutic central effect of LIVIFEM is due to the combined estrogenic, progestogenic and weak androgenic activities of the drug.

LIVIFEM has a moderate gonadotrophin suppressing effect in post-menopausal women.

The peripheral effect of LIVIFEM is the combination of hormonal activities which exerts a balanced effect and does not stimulate the endometrium in post-menopausal women.

Tibolone, the active ingredient of LIVIFEM, is rapidly and extensively absorbed, appearing in the blood within 30 minutes of oral administration with peak levels between 1,5 and 4 hours. Tibolone is metabolised in the liver and converted to metabolites which are excreted mainly in the faeces and to a lesser extent in the urine. Some metabolites may contribute to the biological effects of the medicine. The elimination half-life of tibolone and active metabolites is less than 2 days, justifying once a day administration.

INDICATIONS

- Symptomatic treatment of hot flushes and associated sweating resulting from natural or surgical menopause.
- Prevention of post-menopausal osteoporosis.
- Improvement of bone-mineral density in patients with established post-menopausal osteoporosis.

CONTRA-INDICATIONS

- Pregnancy and lactation.
- Known or suspected hormone-dependent tumours.
- Known, past or suspected breast cancer - LIVIFEM increased the risk of breast cancer recurrence in a placebo-controlled trial.
- Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer).
- Vaginal bleeding of unknown etiology.
- Untreated endometrial hyperplasia.
- Cardiovascular or cerebrovascular disorders e.g. thrombophlebitis, thromboembolic processes or a history of these conditions.
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism).

- Known thrombophilic disorders e.g. protein C, protein S or antithrombin deficiency (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).
- Any history of thromboembolic disease [e.g. angina, myocardial infarction, stroke or transient ischaemic attack (TIA)].
- Severe liver disease.
- Known hypersensitivity to the active substance or to any of the excipients.
- Porphyria.

WARNINGS AND SPECIAL PRECAUTIONS

LIVIFEM is not intended for contraceptive use.

The use of LIVIFEM should be avoided until 12 months after the last natural menstrual bleed. If LIVIFEM is taken sooner than this, the frequency of irregular bleeding may be increased.

Treatment should be discontinued if signs of thromboembolic processes occur, if results of liver function tests become abnormal or if cholestatic jaundice appears.

Vaginal bleeding may occur during LIVIFEM therapy, because of an apparently stimulated endometrium due to some estrogen production. Normally such bleeding is of short duration. Bleedings commencing after 3 months of treatment, or recurrent or of longer duration should be investigated.

In women changing from another form of hormonal substitution therapy to LIVIFEM therapy, it is always advisable to induce a withdrawal bleeding with a progestogen before starting LIVIFEM.

Tibolone has been shown to be teratogenic in experimental animals, and should not be used in pre-menopausal women.

Periodic examinations must be done for endometrial hyperplasia, as well as possible signs of virilisation.

The risks of stroke, breast cancer and endometrial cancer (women with an intact uterus) for each woman should be carefully assessed, in the light of her individual risk factors and bearing in mind the frequency and characteristics of both cancers and stroke, in terms of their response to treatment, morbidity and mortality.

Conditions which need supervision

- If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with LIVIFEM, in particular:
    - leiomyoma (uterine fibroids) or endometriosis
    - a history of, or risk factors for, thromboembolic disorders (see below)
    - risk factors for oestrogen dependent tumours, e.g. 1st degree heredity for breast cancer
    - hypertension
    - liver disorders (e.g. liver adenoma)
    - diabetes mellitus with or without vascular involvement
    - cholelithiasis
    - migraine or (severe) headache
    - systemic lupus erythematosus
    - a history of endometrial hyperplasia (see below)
    - epilepsy

- asthma
- otosclerosis.

Reasons for immediate withdrawal of therapy:

Therapy should be discontinued in case a contra-indication is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache.

Endometrial hyperplasia and cancer

- The available data from randomised controlled trials are conflicting, however, observational studies have consistently shown that women who are prescribed LIVIFEM in normal clinical practice are at an increased risk of having endometrial cancer diagnosed. In these studies risk increased with increasing duration of use. LIVIFEM increases endometrial wall thickness, as measured by transvaginal ultrasound.

The endometrial cancer risk is about 5 in every 1 000 women with a uterus not using HRT or LIVIFEM.

The randomised placebo controlled trial that included women who had not been screened for endometrial abnormalities at baseline, and therefore reflected clinical practice, identified the highest risk of endometrial cancer, (LIFT study, mean age 68 years). In this study no cases of endometrial cancer were diagnosed in the placebo group (n=1 773) after 2,9 years compared with 4 cases of endometrial cancer in the tibolone group (n=1 746). This corresponds to a diagnosis of 0,8 additional cases of endometrial cancer in every 1 000 women who used LIVIFEM for one year in this study.

Breast cancer

- Evidence with respect to breast cancer risk in association with LIVIFEM is inconclusive. The Million Women Study (MWS) has identified a significant increase in the risk of breast cancer in association with use of the 2,5 mg dose. This risk became apparent within a few years of use and increased with duration of intake, returning to baseline within a few (at most five) years after stopping treatment. These results could not be confirmed in a study using the General Practice Research Database (GPRD).

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestogen therapy for more than 5 years.
- Any increased risk in users of oestrogen-only and LIVIFEM therapy is substantially lower than that seen in users of oestrogen-progestogen combinations.
- The level of risk is dependent on the duration of use.
- Results of the largest epidemiological study (MWS) are presented.

Table 2 Million Women study – Estimated additional risk of breast cancer after 5 years use

Age range (years)	**Additional cases per 1 000 never-users of HRT over a 5 year period *2**	**Risk ratio and 95 % CI #**	**Additional cases per 1 000 HRT users over 5 years (95 % CI)**
Oestrogen only HRT			
50 to 65	9 to 12	1,2	1 to 2 (0 to 3)
Combined oestrogen-progestogen			
50 to 65	9 to 12	1,7	6 (5 to 7)
Tibolone			

50 to 65	9 to 12	1,3	3 (0 to 6)
#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration of use. *Taken from baseline incidence rates in developed countries.			

Ovarian cancer

- Ovarian cancer is much rarer than breast cancer. Long-term (at least 5 to 10 years) use of oestrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer (see **"SIDE EFFECTS"**). Some studies including the Women's Health Initiative (WHI) trial suggest that the long-term use of combined HRTs may confer a similar, or slightly smaller risk (see **"SIDE EFFECTS"**). In the Million Women Study it was shown that the relative risk for ovarian cancer with use of LIVIFEM was similar to the risk associated with use of other types of HRT.

Venous thromboembolism

- Oestrogen or oestrogen-progestogen HRT is associated with a 1,3 to 3 fold risk of developing venous thromboembolism i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see **"SIDE EFFECTS"**). In an epidemiological study using a UK database, the risk of VTE in association with LIVIFEM was lower than the risk associated with conventional HRT, but only a small proportion of women were current users of LIVIFEM and a small increase in risk compared with non-use cannot be excluded.
- Generally recognised risk factors for VTE include use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m^2), pregnancy/postpartum period, systemic lupus erythematosus (SLE), **and cancer**. There is no consensus about the possible role of varicose veins in VTE. As in all post-operative patients, scrupulous attention should be given to prophylactic measures that need to be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery,

temporarily stopping HRT or LIVIFEM 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.

- Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. HRT is therefore contra-indicated in these patients (see **"CONTRA-INDICATIONS"**).
- In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening). If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g. antithrombin, protein S or protein C deficiencies or a combination of defects) HRT or LIVIFEM is contra-indicated.
- Women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT or LIVIFEM.
- If VTE develops after initiating therapy, the medicine should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD)

- There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestogen or oestrogen-only HRT. In an epidemiological study using the GPRD no evidence was found of protection against myocardial infarction in post-menopausal women who received LIVIFEM.
- Ischaemic stroke.
- LIVIFEM increases the risk of ischaemic stroke from the first year of treatment. The baseline risk of stroke is strongly age-dependent and so the effect of LIVIFEM is greater with older age.

Risk of ischaemic stroke

- The relative risk of ischaemic stroke is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of ischaemic stroke in women who use HRT or LIVIFEM will increase with age.
- A 2,9 year randomised controlled study has estimated a 2,2-fold increase in the risk of stroke in women (mean age 68 years) who used 1,25 mg tibolone (28/2 249) compared with placebo (13/2 257). The majority (80 %) of strokes were ischaemic.
- The baseline risk of stroke is strongly age-dependent. Thus, the baseline incidence over a 5 year period is estimated to be 3 per 1 000 women aged 50 to 59 years and 11 per 1 000 women aged 60 to 69 years.
- For women who use LIVIFEM for 5 years, the number of additional cases would be expected to be about 4 per 1 000 users aged 50 to 59 years, and 13 per 1 000 users aged 60 to 69 years.

Other adverse reactions have been reported in association with oestrogen and oestrogen-progestogen treatment:

- Long term use of oestrogen-only and combined oestrogen-progestogen HRT has been associated with an increased risk of ovarian cancer. In the Million Women Study 5 years of HRT resulted in 1 extra case per 2 500 users. This study showed that the relative risk for ovarian cancer with LIVIFEM was similar to the risk with other types of HRT.
- HRT is associated with a 1, 3 to 3-fold increased relative risk of developing venous thromboembolism i.e. deep vein thrombosis and pulmonary embolism. The occurrence of such an event is more likely in the first year of using HRT. Results of the WHI studies are presented:

Age range (years)	Incidence per 1 000 women in placebo arm over 5 years	Risk ratio and 95 % CI	Additional cases per 1 000 HRT users
Oral oestrogen-only *4			
50 to 59	7	1,2 (0,6 to 2,4)	1 (-3 to 10)
Oral combined oestrogen-progestogen			
50 to 59	4	2,3 (1,2 to 4,3)	5 (1 to 13)

*4 Study in women with no uterus

- The risk of coronary artery disease is increased in users of combined oestrogen-progestogen HRT over the age of 60. There is no evidence to suggest that the risk of myocardial infarction with LIVIFEM is different to the risk with other HRT.
- Gall bladder disease
- Skin and subcutaneous disorders: Chloasma, erythema multiforme, erythema nodosum, vascular purpura.
- Probable dementia over the age of 65.

Other conditions

- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Effects on ability to drive and use machines

LIVIFEM is not known to have any effects on alertness and concentration.

INTERACTIONS

No examples of interaction between LIVIFEM and other medicines have been reported in clinical practice. However, the following potential interactions should be considered on a theoretical basis:

- Enzyme-inducing compounds such as barbiturates, carbamazepine, hydantoins and rifampicin may enhance the metabolism of tibolone and thus decrease its therapeutic effect.
- Since tibolone may increase blood fibrinolytic activity (lower fibrinogen levels; higher ATIII, plasminogen and fibrinolytic activity values), it may enhance the effect of anticoagulants. Therefore the simultaneous use of LIVIFEM and warfarin should be monitored, especially when starting or stopping concurrent LIVIFEM treatment, and the warfarin dose should be appropriately adjusted.

Herbal preparations containing St.John's wort (*Hypericum perforatum*) may induce the metabolism of oestrogens and progestogens via CYP3A4. Clinically, an increased metabolism of oestrogens and progestogens may lead to decreased effect and changes in the uterine bleeding profile.

PREGNANCY AND BREASTFEEDING

LIVIFEM is contra-indicated during pregnancy. If pregnancy occurs during medication with LIVIFEM, treatment should be withdrawn immediately.

LIVIFEM is contra-indicated during breastfeeding.

DOSAGE AND DIRECTIONS FOR USE

The dosage is 1 tablet per day. A missed dose should be taken as soon as remembered, unless it is more than 12 hours overdue. In the latter case, the missed dose should be skipped and the next dose should be taken at the normal time.

Improvement of symptoms generally occurs within a few weeks, but optimal results are obtained when therapy is continued for at least 3 months.

Administration: LIVIFEM tablets should be swallowed whole with some water or other drink, preferably at the same time each day.

Starting LIVIFEM

Women experiencing a natural menopause should commence treatment with LIVIFEM at least 12 months after their last natural bleed. In case of a surgical menopause, treatment with LIVIFEM may commence immediately.

Any irregular/unscheduled vaginal bleeding, either on or off HRT, for which there is no obvious cause, should be investigated before starting LIVIFEM.

SIDE EFFECTS

This section describes undesirable effects which were registered in 21 placebo controlled studies (including the LIFT study), with 4 079 women receiving therapeutic doses (1,25 or 2,5 mg) of LIVIFEM and 3 476 women receiving placebo. The duration of treatment in these studies ranged from 2 months to 4,5 years. **Table 1** shows the undesirable effects that occurred statistically significantly more frequently during treatment with LIVIFEM than with placebo.

Table 1 Undesirable effects of LIVIFEM

System organ class	**Common** **> 1 %, < 10 %**	**Uncommon** **> 0,1 %, < 1 %**
Gastrointestinal disorders	Lower abdominal pain	
Skin and subcutaneous disorders	Abnormal hair growth	Acne
Reproductive system and breast disorders	Vaginal discharge Endometrial wall thickening	Breast discomfort Fungal infection Vaginal mycosis

	Post-menopausal haemorrhage Breast tenderness Genital pruritus Vaginitis candidiasis Vaginal haemorrhage Pelvic pain Cervical dysplasia Genital discharge Vulvovaginitis	Nipple pain
Investigations	Weight increase Abnormal Cervical smear*	Amnesia

* The majority consisted of benign changes. Cervix pathology (cervical carcinoma) was not increased with tibolone compared to placebo.

In market use other undesirable effects that have been observed include: Dizziness, rash, pruritus, seborrheic dermatosis, headache, migraine, visual disturbances (including blurred vision), gastrointestinal upset, depression, edema, effects on the musculoskeletal system such as arthralgia or myalgia, and changes in liver function parameters.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

In cases of acute overdose nausea, vomiting and vaginal bleeding in females may occur. No specific antidote is known. Symptomatic treatment can be given if necessary.

IDENTIFICATION

A white, round and flat tablet with bevelled edges, coded MK above 2 on one side and Organon and a star on the reverse side.

PRESENTATION

LIVIFEM Tablets are packed in push-through strips of 28 tablets each containing 2,5 mg of tibolone.

Packs contain one strip.

STORAGE INSTRUCTIONS

Store at or below 25 °C. Protect from light and moisture.

Keep out of reach of children.

REGISTRATION NUMBER

V/21.5.4/55

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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