Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Livial 2.5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5mg of tibolone.

Excipients: Contains lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Product imported from the UK:
White, round and flat tablets with bevelled edges coded “MK” above “2” on one side and “Organon” and a star on the reverse side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of estrogen deficiency symptoms in postmenopausal women, more than one year after menopause.

Second line therapy for prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.

For all women the decision to prescribe tibolone should be based on an assessment of the individual patient’s overall risks and, particularly in the over 60s, should include consideration of the risk of stroke (see sections 4.4 and 4.8).

4.2 Posology and method of administration

The dosage is one tablet per day. No dose adjustment is necessary for the elderly. The tablets should be swallowed with some water or other drink, preferably at the same time every day.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also section 4.4) should be used.

A separate progestogen should not be added with Livial treatment.

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

Any irregular / unscheduled vaginal bleeding, either on or off HRT, should be investigated to exclude malignancy before starting Livial (see section 4.3)

Switching from a sequential or continuous combined HRT preparation
If changing from a sequential HRT preparation, treatment with Livial should start the day following completion of the prior regimen. If changing from a continuous-combined HRT preparation, treatment can start at any time.

Missed dose
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. Missing a dose may increase the likelihood of breakthrough bleeding and spotting.

4.3 Contraindications

- Pregnancy and lactation
- Known, past or suspected breast cancer - tibolone increased the risk of breast cancer recurrence in a placebo-controlled trial
- Known or suspected estrogen-dependent maliginant tumors (e.g. endometrial cancer)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Any history of arterial thromboembolic disease (e.g angina, myocardial infarction stroke or TIA)
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal
- Known hypersensitivity to the active substance or to any of the excipients
- Porphyria

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, tibolone should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and tibolone should only be continued as long as the benefit outweighs the risk.
The risks of stroke, breast cancer and in women with an intact uterus, endometrial cancer (see below and section 4.8) 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 morality.

Medical examination/follow-up
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 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 (see ‘Breast cancer’ below). Investigations, including mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

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 Livial, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- A history of, or risk factors for, thromboembolic disorders (see below)
- Risk factors for estrogen dependent tumors, 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 erythematosis
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

Reasons for immediate withdrawal of therapy:
Therapy should be discontinued in case a contraindication 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 cancer
- The available data from randomized controlled trials are conflicting, however, observational studies have consistently shown that women who are prescribed tibolone in normal clinical practice are at an increased risk of having endometrial cancer diagnosed (see Section 4.8). In these studies risk increased with increasing duration of use. Tibolone increases endometrial wall thickness, as measured by transvaginal ultrasound.
- Break-through bleeding and spotting may occur during the first months of treatment (see section 5.1). Women should be advised to report any break-through bleeding or spotting if it is still present after 6 months of treatment, if it starts beyond that time or if it continues after treatment has been discontinued. The woman should be referred for gynecological investigation, which is likely to include endometrial biopsy to exclude endometrial malignancy.

Breast cancer
- Evidence with respect to breast cancer risk in association with tibolone is inconclusive. The Million Women Study (MWS) has identified a significant increase in the risk of breast cancer in association with use of the 2.5mg 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, see section 4.8. These results could not be confirmed in a study using the General Practitioners Research Database.

Venous thromboembolism
- Estrogen or estrogen-progestogen HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomized controlled trial and epidemiological studies found a two- to threefold higher risk for users compared with non-users. For non-users it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged between 60-69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate = 4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate = 9) per 1000 women aged 60-69 years. The occurrence of such an event is more likely in the first year of HRT than later. It is unknown whether Livial carries the same level of risk.
- Generally recognized risk factors for VTE include a personal history or family history, severe obesity (BMI > 30 kg/m^2) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.
- Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.
- The risk of VTE may be temporarily increased with prolonged immobilization, major trauma or major surgery. As in all postoperative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilization is liable to follow elective surgery, particularly abdominal surgery or orthopedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT 4 to 6 weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilized.
- If VTE develops after initiating therapy, the drug 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, dyspnea).

In an epidemiological study using a UK database, the risk of VTE in association with tibolone was lower than the risk associated with conventional HRT, but only a small proportion of women were current users of tibolone and a small increase in risk compared with non-use cannot be excluded.

Coronary artery disease (CAD)

- There is no evidence from randomized controlled trials of cardiovascular benefit with continuous combined conjugated estrogens and medroxyprogesterone acetate (MPA). Two large clinical trials (WHI and HERS i.e. Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomized controlled trials examining effects in cardiovascular morbidity or mortality. Therefore, it is uncertain whether these findings also extend to other HRT products.

In an epidemiological study using the GPRD no evidence was found of protection against myocardial infarction in postmenopausal women who received tibolone.

Stroke

- Tibolone increases the risk of ischaemic stroke from the first year of treatment (see section 4.8). The baseline risk of stroke is strongly age-dependent and so the effect of tibolone is greater with older age.

Ovarian cancer

- Long-term (at least 5-10 years) use of estrogen-only HRT products in hysterectomized women has been associated with an increased risk of ovarian cancer in some epidemiological studies. It is uncertain whether long-term use of combined HRT confers a different risk than estrogen-only products.

In the Million Women Study it was shown that the relative risk for ovarian cancer with use of tibolone was similar to the risk associated with use of other types of HRT.

Other conditions

- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- Treatment with Livial results in a marked dose-dependent decrease in HDL- cholesterol, total (from -16.7% with a 1.25 mg dose to -21.8% for the 2.5 mg dose after 2 years). Total triglycerides and lipoprotein(a) levels were also reduced. The decrease in total cholesterol and VLDL-C levels was not dose-dependent. Levels of LDL-C were unchanged. The clinical implication of these findings is not yet known
- Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.
- Women with pre-existing hypertriglyceridemia should be followed closely during estrogen replacement or HRT, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition.
- Treatment with Livial results in a very minor decrease of thyroid binding globulin (TBG) and total T4. Levels of total T3 are unaltered. Livial decreases the level of sex-hormone-binding globulin (SHBG), whereas the levels of corticoid binding globulin (CBG) and circulating cortisol are unaffected.
- There is no conclusive evidence for improvement of cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined conjugated estrogens and MPA after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent use with certain antibiotics, anti-epileptic drugs or sedatives may reduce the effectiveness of tibolone.

Since tibolone may increase blood fibrinolytic activity it may enhance the effect of anticoagulants. This effect has been demonstrated with warfarin. Caution should therefore be exercised during the simultaneous use of Livial and anticoagulants, especially when starting or stopping concurrent Livial treatment.

An *in vivo* study showed that simultaneous treatment of tibolone affects pharmacokinetics of the cytochrome P450 3A4 substrate midazolam to a moderate extent. Based on this, drug interactions with other CYP3A4 substrates might be expected, however, the clinical relevance is dependent on the pharmacological and pharmacokinetic properties of the substrate involved.

4.6 Fertility, pregnancy and lactation

Livial is contraindicated during pregnancy (see Section 4.3). if pregnancy occurs during medication with Livial, treatment should be withdrawn immediately. For Livial no clinical data on exposed pregnancies are available. Studies in animals have shown reproductive toxicity (see Section 5.3). The potential risk for humans is unknown.

Livial is contraindicated during lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

Livial has no effect on the ability to drive and use machines.

4.8 Undesirable effects

This section describes undesirable effects, which were registered in 21 placebo-controlled studies (including the LIFT study) with 4079 women receiving therapeutic doses (1.25 or 2.5mg) of tibolone and 3476 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 tibolone than with placebo.

Table 1 Undesirable effects of Livial

System organ class	**Common >1%,<10%**	**Uncommon >0.1%,<1%**
Gastro-intestinal disorders	Lower abdominal pain	
Skin and subcutaneous tissue disorders	Abnormal hair growth	Acne
Reproductive system and breast disorders	Vaginal discharge Endometrial wall thickening Postmenopausal haemorrhage Breast tenderness Genital pruritus Vaginal candidiasis Vaginal haemorrhage Pelvic pain Cervical dysplasia Genital discharge Vulvovaginitis	Breast discomfort Fungal infection Vaginal mycosis Nipple pain
Investigations	Weight increase Abnormal cervical smear*	

* 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.

Breast cancer

The MWS reported that, compared with never users, the use of various types of estrogen-progestogen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95%CI: 1.88-2.12) than use of estrogens alone (RR = 1.30, 95%CI: 1.21-1.40) or use of 2.5 mg tibolone (RR=1.45; 95%CI 1.25-1.68).

- **For women not using HRT or tibolone, about 32 in every 1000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years.**
- For 1000 current or recent users of HRT, the number of *additional* cases during the corresponding period will be

- For users of *estrogen-only* replacement therapy,
between 0 and 3 (best estimate = 1.5) for 5 years' use
between 3 and 7 (best estimate = 5) for 10 years' use.

- For users of *estrogen-progestogen* combined HRT,
between 5 and 7 (best estimate = 6) for 5 years' use
between 18 and 20 (best estimate = 19) for 10 years' use.
For women who use tibolone the number of additional cases of breast cancer was comparable with that for estrogen-only use.

Endometrial cancer

The randomized 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 case of endometrial cancer in every 1000 women who used tibolone for one year in this study (see section 4.4).

Ovarian cancer
Long term use of estrogen-only and combined estrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer. In the Million Women Study 5 years of HRT resulted in 1 extra case per 2500 users. This study showed that the relative risk for ovarian cancer with tibolone was similar to the risk with other types of HRT.

Stroke

A 2.9 year randomized controlled study has estimated a 2.2 fold increase in the risk of stroke in women (mean age 68 years) who used 1.25mg tibolone (28/2249) compared with placebo (13/2257). The majority (80%) of strokes were ischarmic.
The baseline risk of stroke is strongly age- dependent. Thus the baseline incidence over a 5 year period is estimated to be 3 per 1000 women aged 50-59 years and 11 per 1000 women aged 60-69 years.
For women who use tibolone for 5 years, the number of additional cases would be expected to be about 4 per 1000 users aged 50-59 years and 13 per 1000 users aged 60-69 years.

Risk of coronary artery disease

The risk of coronary artery disease is slightly increased in users of combined oestrogen-progestagen HRT over the age of 60 (see section 4.4). There is no evidence to suggest that the risk of myocardial infarction with tibolone is different to the risk with other HRT

Other adverse reactions have been reported in association with estrogen-progestogen treatment:
- Estrogen-dependent neoplasms benign and malignant, e.g., endometrial carcinoma
- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among HRT users than among non-users. For further information, see sections 4.3 and 4.4.
- Myocardial infarction and stroke
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia (see section 4.4)

4.9 Overdose

The acute toxicity of Livial is very low, therefore toxic symptoms will not occur when several tablets are taken simultaneously, possibly in this situation gastric disturbances may occur. Specific treatment is not required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: G03CX01

Following oral administration tibolone is rapidly metabolised into three compounds which contribute to the pharmacological effects of Livial. Two of these metabolites (3α-OH-tibolone and 3β-OH-tibolone) have estrogenic-like activies, whereas the third metabolite (Δ4-isomer of tibolone) has progestogenic and androgenic-like activities..

Livial substitutes for the loss of estrogen production in postmenopausal women and alleviates menopausal symptoms. Livial prevents bone loss following menopause or ovariectomy.

Clinical trial information of Livial:

▪ Relief of estrogen-deficiency symptoms

- Relief of menopausal symptoms generally occurs during the first few weeks of treatment.

▪ Effects on the endometrium and bleeding patterns

– There have been reports of endometrial hyperplasia and endometrial cancer in patients treated with tibolone (see section 4.4 and 4.8).

- Amenorrhea has been reported in 88.4% of the women using tibolone 2.5 mg after 12 months treatment. Breakthrough bleeding and/or spotting has been reported 32.6% of the women during the first three months of treatment and in 11.6% of women after 11-12 months of use.

▪ Prevention of osteoporosis

– Estrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass. Protection appears to be effective for as long as treatment is continued. After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women.

- In the LIFT study, tibolone reduced the number of women (mean age 68 years) with new vertebral fractures compared to placebo during the 3 years of treatment (ITT: tibolone to placebo odds ratio 0.57; 95% Cl [0.42, 0.78]).

– After 2 years of treatment with Livial (2.5 mg), the increase in lumbar spine bone mineral density (BMD) was 2.6 ± 3.8%. The percentage of women who maintained or gained BMD in lumbar zone during treatment was 76%. A second study confirmed these results.

– Livial (2.5 mg) also had an effect on hip BMD. In one study, the increase after 2 years was 0.7 ± 3.9% at the femoral neck and 1.7 ± 3.0% at the total hip. The percentage of women who maintained or gained BMD in the hip region during treatment was 72.5%. A second study showed that the increase after 2 years was 1.3 ± 5.1% at the femoral neck and 2.9 ± 3.4% at the total hip. The percentage of women who maintained or gained BMD in the hip region during treatment was 84.7%.

▪ Effects on the breast

– In clinical studies mammographic density is not increased in women treated with Livial compared to placebo.

5.2 Pharmacokinetic properties

After oral administration, tibolone is rapidly and extensively absorbed. Due to rapid metabolism, the plasma levels of tibolone are very low. The plasma levels of the Δ4-isomer of tibolone are also very low. Therefore some of the pharmacokinetic parameters could not be determined. Peak plasma levels of the 3α-OH and the 3β-OH metabolites are higher but accumulation does not occur.

Table 1 Pharmacokinetic parameters of Livial (2.5 mg)

	tibolone		3α-OH metabolite		3β-OH metabolite		Δ4-isomer	
	SD	MD	SD	MD	SD	MD	SD	MD
C_{max} (ng/ml)	1.37	1.72	14.23	14.15	3.43	3.75	0.47	0.43
$C_{average}$	--	--	--	1.88	--	--	--	--
T_{max} (h)	1.08	1.19	1.21	1.15	1.37	1.35	1.64	1.65
$T_{1/2}$ (h)	--	--	5.78	7.71	5.87	--	--	--
C_{min} (ng/ml)	--	--	--	0.23	--	--	--	--
AUC_{0-24} (ng/ml.h)	--	--	53.23	44.73	16.23	9.20	--	--

SD = single dose; MD = multiple dose

Excretion of tibolone is mainly in the form of conjugated (mostly sulphated) metabolites. Part of the administered compound is excreted in the urine, but most is eliminated via the faeces. The consumption of food has no significant effects on the extent of absorption.

The pharmacokinetic parameters for tibolone and its metabolites were found to be independent of renal function.

5.3 Preclinical safety data

In animal studies, tibolone had anti-fertility and embryotoxic activities by virtue of its hormonal properties. Tibolone was not teratogenic in mice and rats. It displayed teratogenic potential in the rabbit at near-abortive dosages (see section 4.6). Tibolone is not genotoxic under in vivo conditions. Although a carcinogenic effect was seen in certain strains of rat (hepatic tumors) and mouse (bladder tumors), the clinical relevance of this is uncertain.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potato starch
Magnesium stearate
Ascorbyl palmitate
Lactose

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf life expiry date of this product is the date shown on the blister strips and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Do not store above 25ºC. Keep the blister in the outer carton in order to protect from light and moisture.

6.5 Nature and contents of container

An over-labelled cardboard carton containing one blister strip of 28 tablets.
Pack size: 28 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1500/56/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9th April 2010

10 DATE OF REVISION OF THE TEXT

May 2012