Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Livial 2.5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5 mg of tibolone.

Excipients: also includes lactose monohydrate.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

White, round and flat tablets with bevelled edges and a diameter of 6 mm and 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 Livial 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 - Livial increased the risk of breast cancer recurrence in a placebo-controlled trial
- Known or suspected estrogen-dependent malignant tumors (e.g. endometrial cancer)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Known thrombophilic disorders (e.g. protein C, protein S, or anithrombin deficiency, see section 4.4)
- 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, Livial 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 Livial 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 mortality.

Evidence regarding the risks associated with HRT or tibolone in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

Medical examination/follow-up

- Before initiating or reinstituting HRT or tibolone, 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 appropriate imaging tools, e.g. 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
  - 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 erythematosus
- 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 hyperplasia and carcinoma

- The available data from randomized controlled trials are conflicting, however, observational studies have consistently shown that women who are prescribed Livial in normal clinical practice are at an increased risk of having endometrial cancer diagnosed (see also 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

- A meta-analysis of epidemiological studies, including the Million Women Study (MWS), showed a significant increase in the risk of breast cancer in association with use of the 2.5 mg dose. This risk became apparent within 3 years of use and increased with duration of intake, see section 4.8. After stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more. No data for persistence of risk after stopping are available for tibolone, but a similar pattern cannot be ruled out.

Ovarian cancer

- Ovarian cancer is much rarer than breast cancer

Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined oestrogen-progestagen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping. Some other studies, including the Women's Health Initiative (WHI) trial, suggest that the use of combined HRTs may be associated with a similar, or slightly smaller risk (see section 4.8). 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.

Venous thromboembolism

- Estrogen or estrogen-progestogen HRT is associated with a 1.3-3 fold risk of developing venous thromboembolism (VTE), 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 section 4.8). 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.
- Patients with known thrombophilic states have an increased risk of VTE and HRT or tibolone may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).

- Generally recognized risk factors for VTE include use of estrogens, older age, major surgery, prolonged immobilization, 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 postoperative patients, prophylactic measures need to be considered to prevent VTE following surgery If prolonged immobilization is to follow elective surgery, temporarily stopping HRT or tibolone 4 to 6 weeks earlier, is recommended. Treatment should not be restarted until the woman is completely mobilized.

- 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 counseling 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 tibolone is contraindicated.

- Women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT or tibolone.

- 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).

Coronary artery disease (CAD)

- There is no evidence from randomized controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined estrogen-progestagen or estrogen-only HRT. In an epidemiological study using the GPRD no evidence was found of protection against myocardial infarction in postmenopausal women who received tibolone.

Ischaemic 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.

Other conditions

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

- Livial is not intended for contraceptive use.

- 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.

HRT use does not improve cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined or estrogen-only HRT after the age of 65.

4.5 Interaction with other medicinal products and other forms of interactions

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. If necessary, the dose of warfarin should be adjusted.

There is limited information regarding pharmacokinetic interactions with tibolone. 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.

CYP3A4 inducing compounds such as barbiturates, carbamazepine, hydantoins and rifampicin may enhance the metabolism of tibolone and thus affect its therapeutic effect.

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

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 Livial 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 Livial 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 Livial 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 risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined estrogen-progestagen therapy for more than 5 years.
- The increased risk in users of estrogen-only and tibolone therapy is substantially lower than that seen in users of estrogen-progestagen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- 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 1000 never-users of HRT over a 5 year period*2	Risk ratio & 95%CI#	Additional cases per 1000 HRT users over 5 years (95%CI)
Estrogen only HRT			
50-65	9-12	1.2	1-2 (0-3)
Combined estrogen-progestagen			
50-65	9-12	1.7	6 (5-7)
Tibolone			
50-65	9-12	1.3	3 (0-6)
#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration of use.			

Endometrial cancer risk

The endometrial cancer risk is about 5 in every 1000 women with a uterus not using HRT or tibolone.

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 Livial group (n=1,746). This corresponds to a diagnosis of 0.8 additional case of endometrial cancer in every 1000 women who used Livial for one year in this study (see section 4.4).

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 tibolone will increase with age, see section 4.4.
- 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 Livial (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 Livial 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.

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

Ovarian Cancer

Use of estrogen-only or combined estrogen-progestagen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see section 4.4)

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. 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.

In the Million Women Study, taking 5 years of tibolone resulted in 1 extra case per 2500 users (see section 4.4). HRT is associated with a 1.3-3-fold increased relative risk of developing venous - thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HRT (see section 4.4). Results of the WHI studies are presented:

Table 3 WHI Studies - Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users
Oral estrogen-only*4			
50-59	7	1.2 (0.6-2.4)	1 (-3-10)
Oral combined estrogen-progestagen			
50-59	4	2.3 (1.2–4.3)	5 (1-13)

4 *Study in women with no uterus

The risk of coronary artery disease is slightly increased in users of combined estrogen-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.
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia over the age of 65 (see section 4.4)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

The acute toxicity of Livial is very low, therefore toxic symptoms are not expected when several tablets are taken simultaneously. In cases of acture overdose, nausea, vomiting and vaginal bleeding in females may occur. No specific antidote is known. Symptomatic treatment can be given if necessary.

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 activities, whereas the third metabolite (D4-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 Livial (see section 4.4 and 4.8).
- Amenorrhea has been reported in 88% of women using Livial 2.5mg after 12 months of treatment. Breakthrough bleeding and/or spotting has been reported in 32.6% of 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, Livial reduced the number of women (mean age 68 years) with new vertebral fractures compared to placebo during the 3 years of treatment (ITT: Livial to placebo odds ratio 0.57; 95% CI [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 D4-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**		**D4-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 monohydrate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25^{o}C.

Keep the blister in the outer carton.

6.5 Nature and contents of container

The push-through pack is a PVC/A1 blister, consisting of aluminium foil with a heat seal coating and a PVC film.

Each blister strip contains 28 white tablets. The blister is packed in a printed cardboard box together with the package leaflet (1 or 3 blister strips per box).

Not all pack sizes may be marketed.

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 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA23198/021/001

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10 DATE OF REVISION OF THE TEXT

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