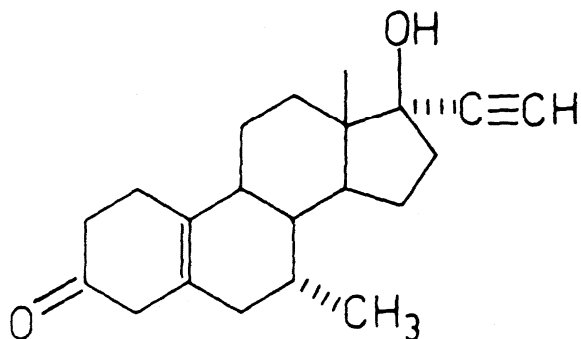


Livial[®]

(i) NAME OF THE DRUG

Livial (tibolone) 2.5 mg tablets

Tibolone



Molecular formula C₂₁H₂₈O₂

Molecular mass 312.45.

[CAS No. 5630-53-5]

Chemical name:

(7 α , 17 α) - 17 - hydroxy-7-methyl-19-norpregn-5 (10)-en-20-yn-3-one.

Other name:

17 α -ethynyl-17-hydroxy-7 α -methyl-5(10)-estren-3-one.

Pharmaceutical Form

Tablets, each containing 2.5 mg of the steroid tibolone.

(ii) DESCRIPTION

Tibolone exists as white to almost white crystals or crystalline powder. Tibolone is related to and derived from naturally occurring steroids. It is optically pure and has the D-configuration. It is practically insoluble in water, aqueous acid or alkali at 20^oC.

(iii) PHARMACOLOGY

Pharmacodynamic properties

ATC code: G03CX01

After oral administration tibolone is rapidly metabolised into three compounds which contribute to the pharmacological effects of Livial. Two of these metabolites (the 3 α OH and 3 β OH metabolite) have predominantly estrogenic activity, a third metabolite (Δ^4 -isomer of tibolone) and the parent compound have predominantly progestagenic and androgenic activities.

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

Livial has various tissue-specific effects. It has estrogenic effects on the vagina, on bone and on the thermoregulatory centres in the brain (hot flashes). Based on *in vitro* data, Livial inhibits the sulphatase enzyme in cultured breast cancer cells thereby reducing the levels of

active oestrogens produced in those cells. Due to local conversion to the Δ^4 -isomer, the endometrial findings have been mainly atrophic or in some cases weakly proliferative, which can in themselves be considered normal endometrial states. Therefore, if vaginal bleeding occurs, this usually results from an atrophic endometrium. Livial also has androgenic effects on certain metabolic and haematological parameters such as a decrease in plasma high density lipoprotein cholesterol, triglycerides and lipoprotein(a), and may increase blood fibrinolytic activity. Livial improves vaginal dryness and vaginal atrophy. There are indications that Livial has effects on mood and libido.

Effects on the endometrium and bleeding patterns

- There have been reports of endometrial hyperplasia and endometrial cancer in patients treated with tibolone (refer **Precautions** and **Adverse Reactions**).
- Amenorrhoea has been reported in 88% of women using tibolone 2.5 mg after 12 months of treatment. Breakthrough bleeding and/or spotting has been reported in 32.6% of women during the first 3 months of treatment, and in 11.6% of women after 11-12 months of use.

Effect on the breast

In clinical studies mammographic density is not statistically significantly increased in women treated with Livial 2.5mg daily compared to placebo but a trend to higher mammographic density was noted for Livial 2.5mg daily.

Pharmacokinetic properties

Following 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 Δ^4 -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		Δ^4 -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 sulfated) metabolites. Part of the administered compound is excreted in the urine, but most is eliminated via the feces.

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.

Clinical Trials Experience

Relief of oestrogen deficiency symptoms

Two pivotal, multicentre, randomized, double-blind studies assessed the effects of tibolone on climacteric complaints. One of these studies was a placebo-controlled study and assessed the effects on hot flushes and sweats in groups of about 150 subjects after a 12-week treatment with various doses of tibolone and placebo. The 2.5 mg dose appeared to be

the optimal dose for relieving hot flushes, sweats and other climacteric complaints. The other study was an active controlled study that compared the effects of a 48-week treatment of 2.5 mg tibolone with that of a continuous combined estradiol/norethisterone acetate combination in groups of about 220 post-menopausal subjects. Tibolone significantly relieved the climacteric symptoms (hot flushes, sweats, vaginal dryness and rating scores on well-being); the effects appeared to be similar to that of the continuous combined HT-preparation. The efficacy of tibolone on the climacteric symptoms was confirmed in three Organon-sponsored studies and in published studies. In addition to the positive effects on climacteric complaints, tibolone also has an effect on mood and libido.

Prevention of osteoporosis

In two identical pivotal, multicentre, randomised, double-blind, placebo-controlled studies four doses of tibolone or placebo were given for 2 years to groups of about 75 women per dose and per study to assess the efficacy for preventing post-menopausal bone mineral density loss, safety and acceptability. In these studies, the bone mineral density measured with DEXA was significantly increased at all sites (spine, femoral neck, trochanter and Ward's, and distal radius) with the 2.5 mg dose compared to the placebo-groups. The results on BMD were confirmed by the results on the biochemical markers of bone turnover, showing that tibolone reduces the markers for bone resorption to a greater extent than the markers for bone formation. The efficacy of tibolone on bone was confirmed in 11 Organon-sponsored studies and many other studies published in literature.

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%CI [0.42, 0.78]. Because this study used only tibolone 1.25mg daily versus placebo, its contribution to the risk: benefit profile of tibolone 2.5 mg daily in the prevention of osteoporosis is unknown.

(iv) INDICATIONS

- Treatment of symptoms resulting from the natural or surgical menopause in post menopausal women. Women above 60 years of age should only start with Livial treatment when they are intolerant of or contraindicated for other medicinal products approved for the treatment of oestrogen deficiency symptoms.
- Prevention of bone mineral density loss in postmenopausal women at high risk of future osteoporotic fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of bone mineral density loss.

After careful selection of users, Livial should be prescribed for the shortest duration consistent with treatment goals.

Review the need for continuation of treatment after 6 months, taking into account the risk-benefit ratio for the individual user at that moment (including cardiovascular disease and breast cancer, refer **Clinical Trials** and **PRECAUTIONS**). Livial should only be continued for as long as the benefit outweighs the risks.

(v) 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 malignant tumours (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 any of the excipients
- Porphyria

(vi) PRECAUTIONS

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.

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. The risks of stroke, breast cancer and, in women with an intact uterus, endometrial cancer (see below and **ADVERSE REACTIONS**) 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.

Medical examination/follow-up

- Before initiating or reinstating 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 oestrogen 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 cancer

- The available data from clinical trials are conflicting, however, observational studies suggest that women who are prescribed tibolone in normal clinical practice may be at an increased risk of having endometrial cancer diagnosed. The risk increases with increasing duration of use but shows no significant increase during the first 2-3 years of use (see section **ADVERSE REACTIONS**). Tibolone increases endometrial wall thickness, as measured by transvaginal ultrasound.
- Break-through bleeding and spotting may occur during the first months of treatment (refer **PHARMACODYNAMIC PROPERTIES**). 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.
- The risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The addition of a progestogen to oestrogen-only HRT for at least 12 days per cycle in non-hysterectomized women greatly reduces this risk.

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 2.5 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. However, a study using the General Practitioners' Research Database (GPRD), did not show an increased risk (see section **ADVERSE REACTIONS**). The THEBES study provided comparisons with continuous daily doses of conjugated oestrogens 0.625mg and medroxyprogesterone acetate 2.5mg) risk (see section **ADVERSE REACTIONS**).

Venous thromboembolism

- Oestrogen or oestrogen-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/m²) 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 HRT use.

- 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).

Coronary artery disease (CAD)

- There is no evidence from randomized controlled trials of cardiovascular benefit with continuous combined conjugated oestrogens and medroxyprogesterone acetate (MPA). Two large clinical trials (WHI and HERS i.e. Heart and Oestrogen/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.

Stroke

- Tibolone increases the risk of ischaemic stroke from the first year of treatment (refer **ADVERSE REACTIONS**). 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 oestrogen-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 to a different risk than oestrogen-only products.

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 dose-dependent decrease in HDL-cholesterol, total triglycerides and lipoprotein(a) levels. The decrease in total cholesterol and VLDL-C levels was not dose-dependent. Levels of LDL-C were unchanged.
- Oestrogens 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 oestrogen replacement or HRT, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen 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 oestrogens and MPA after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products.

Carcinogenicity/mutagenicity

Tibolone treatment, similar to treatment with other sex hormones, in rodent studies demonstrated an association with the development of a range of tumours in long-term oral carcinogenicity studies. These included pituitary adenomas, mammary carcinomas and fibroadenomas, hepatic adenomas, uterine carcinoma, stromal polyps and stromal sarcoma, and carcinomas of the urinary bladder and testes. Tibolone did not show any evidence of genotoxicity in assays for gene mutations, chromosomal damage and DNA damage.

Use in pregnancy

Category D

Livial is contraindicated in women of reproductive potential including the women in the perimenopausal period. Studies in animals have shown that tibolone crosses the placenta in rabbits, and is teratogenic. Oral treatment of rats with tibolone during the period of organogenesis was associated with foetal microphthalmia (doses ≥ 0.7 mg/kg/day). In rabbits, a range of abnormalities were observed following oral maternal tibolone treatment (doses ≥ 0.7 mg/kg/day), including hydrocephaly, cleft palate, umbilical hernia, limb flexure and malrotation, bilateral microphthalmia and ocular opacity. A no-effect dose could not be demonstrated in either species. No evidence for teratogenic activity was observed in mice. Systemic exposure to tibolone and its metabolites in the rat study (not measured in the rabbit or mouse study) was substantially lower than the anticipated human exposure.

Use in lactation

Livial is contraindicated in lactating women.

Interaction with other medicines

Since Livial 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 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.

Effects on ability to drive and use machines

As far as is known Livial has no effect on alertness and concentration.

(vii) ADVERSE REACTIONS

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 2.5 mg) of tibolone and 3476 women receiving placebo. The duration of treatment in these studies ranged from 2 months to 4.5 years. Table 2 shows the undesirable effects that occurred statistically significantly more frequently during treatment with tibolone than with placebo.

Table 2. Adverse effects of Livial

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

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

The MWS has estimated, from the known average incidence of breast cancer in developed countries, that:

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 *oestrogen-only* replacement therapy,
 - o between 0 and 3 (best estimate = 1.5) for 5 years' use
 - o between 3 and 7 (best estimate = 5) for 10 years' use.
- For users of *oestrogen-progestogen* combined HRT,
 - o between 5 and 7 (best estimate = 6) for 5 years' use
 - o between 18 and 20 (best estimate = 19) for 10 years' use.

For women who use tibolone the number of additional cases of breast cancer is comparable with that for estrogen-only use.

A GPRD study reported that, compared with never users, the rate of breast cancer was not elevated in subjects who exclusively used unopposed oestrogens (RR 0.97: 95% CI: 0.86 – 1.09) or tibolone (RR 0.86: 95% CI: 0.65 – 1.13). However, the rate was significantly increased in subjects who used combined oestrogen-progestogen HRT (adjusted rate ratio [RR] 1.33: 95% CI: 1.23 – 1.44), which further increased with longer duration of use.

In the THEBES study, a multi-national, multicentre, randomized, double blind, parallel group, active controlled, comparative study in which 807 healthy postmenopausal women, aged 45 to 65 years, were randomised to tibolone 1.25 mg, 816 to tibolone 2.5 mg and 1,617 to continuous CE/MPA (conjugated oestrogens 0.625 mg and medroxyprogesterone acetate 2.5 mg) to study various safety endpoints. Breast cancer was diagnosed more with tibolone

than with CE/MPA: the tibolone 2.5 mg daily group 8 adjudicated cases, tibolone 1.25 mg daily had 2 cases and CE/MPA had 8 cases. Tibolone 2.5 mg tablet had a RR (95% CI) of 2.47 (0.88 to 7.19) compared with CE/MPA and 4.82 (1.03 to 45.21) compared with the 1.25 mg dosage form. The study cannot provide comparisons against no treatment as there was no placebo arm. The study was not specifically designed to provide these comparisons but these findings do underscore the need to observe the relevant Precautions for use.

Endometrial cancer

In the randomised placebo controlled trial that identified the highest risk of endometrial cancer (LIFT 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 (refer **PRECAUTIONS**).

Stroke

- 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 (28/2249) compared with placebo (13/2257). 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 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.

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

- Oestrogen-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, (refer **CONTRAINDICATIONS** and **PRECAUTIONS**).
- Myocardial infarction
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia (Refer **PRECAUTIONS**)

(viii) DOSAGE AND METHOD OF ADMINISTRATION

Treatment of symptoms resulting from the natural or surgical menopause

The recommended dose is 2.5 mg once daily.

Prevention of post-menopausal bone mineral density loss:

The recommended dose is 2.5 mg once daily.

The tablets should be swallowed with some water or other drink, preferably at the same time of day. Improvement of symptoms generally occurs within a few weeks, but optimal results are obtained when therapy is continued for at least 3 months.

For initiation and continuation of treatment of post menopausal symptoms, the lowest effective dose for the shortest duration (refer **PRECAUTIONS**) should be used.

Review the need for continuation of treatment after 6 months, taking into account the risk-benefit ratio for the individual user at that moment.

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 (refer **CONTRAINDICATIONS**).

Switching from combined or oestrogen only hormone replacement therapy (HT)

In women with a uterus who change from an oestrogen-only preparation, a withdrawal bleed should be induced before starting Livial. If changing from a sequential HT preparation, treatment with Livial should start after the progestagen phase has been completed. If changing from a continuous-combined HT preparation, treatment can start at any time. If abnormal vaginal bleeding is the reason for switching from combined HT, it is advised to investigate the cause of bleeding before starting Livial.

Missed tablets

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.

Monitoring Advice

As for all steroids with hormonal activity, yearly medical examination particularly of the breasts and pelvic areas is advisable. Review the need for continuation of treatment after 6 months (refer to Precautions and Indications).

The occurrence of vaginal bleeding or spotting soon after starting treatment with Livial may be due to the residual effects of endogenous or exogenous oestrogens. Bleeding commencing after three months of treatment, or recurrent or persistent bleeding should be investigated.

(ix) OVERDOSAGE

The acute toxicity of tibolone in animals is very low. Therefore, toxic symptoms are not expected to occur if several tablets are taken simultaneously. In cases of acute overdose, nausea, vomiting, and withdrawal bleeding in females may develop. No specific antidote is known. Symptomatic treatment can be given if necessary.

(x) PRESENTATION

Livial tablets 2.5 mg are 6 mm diameter white, round and flat with beveled edge, coded MK above 2 on one side and Organon and a star on the reverse side.

Livial tablets 2.5 mg are packed in push-through strips of clear polyvinyl chloride film and aluminium foil containing a heat seal coating on the side in contact with the tablets and white on the other side.

The following packages are available: 1 or 3* push-through strips with 28 white tablets each containing 2.5 mg tibolone.

Active component

Tibolone

List of excipients

Livial tablets 2.5 mg contain potato starch, magnesium stearate, ascorbyl palmitate and

lactose.

Incompatibilities

No incompatibilities have been found.

Storage conditions and Shelf-life

The shelf life for Livial tablets 2.5 mg is 2 years, if stored in the dark and kept dry below 25⁰C. The tablets should not be used after the expiry date on the package.

(xi) MEDICINE CLASSIFICATION

Prescription Medicine

(xii) NAME AND ADDRESS OF SPONSOR

Schering-Plough

A division of Schering-Plough Animal Health Ltd

36 Kitchener St

Auckland

Telephone: (09) 375 9210

Date of Preparation:

07 September 2009

(Based on Aust PI dated 27 Aug 2009)