Livial 2.5 mg tablets

tibolone

PRESCRIBING INFORMATION
Refer to Summary of Product Characteristics (SPC) before prescribing

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to MSD (tel: 01992-467272).

PRESENTATION
Livial 2.5 mg tablets containing 2.5 mg of tibolone.

USES
Treatment of oestrogen deficiency symptoms in postmenopausal women, more than one year after menopause. Prevention of osteoporosis in postmenopausal women at high risk of future fractures, intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis. The decision to prescribe Livial should be based on an assessment of the individual’s overall risks and, particularly in the over 60s, should include consideration of the risk of stroke.

DOSAGE AND ADMINISTRATION
One tablet per day. No dose adjustment necessary in the elderly. Tablets should be swallowed with 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 should be used. A separate progestogen should not be added with Livial treatment. 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. Women treated with gonadotrophin releasing hormone (GnRH) analogues may commence treatment with Livial immediately. If changing from a sequential HRT preparation, start Livial the day following completion of the prior regimen. If changing from a continuous-combined HRT preparation, treatment can start at any time. Any irregular vaginal bleeding should be investigated to exclude malignancy before starting Livial.

CONTRAINDICATIONS
Pregnancy and lactation, known, past or suspected breast cancer, known or suspected oestrogen-dependent malignant tumours, undiagnosed genital bleeding, untreated endometrial hyperplasia, previous or current venous thromboembolism (DVT, PE), known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency) 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 remain abnormal, known hypersensitivity to the active substance or to any of the excipients, porphyria.

PRECAUTIONS
For the treatment of postmenopausal symptoms, Livial should only be initiated for symptoms that adversely affect quality of life. The risks of stroke, breast cancer and, in women with an intact uterus, endometrial cancer, should be carefully assessed for each woman. 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, the balance of benefits and risks for these women may be more favourable than in older women.
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 / warnings for use. Periodic check-ups are recommended during treatment. The patient should be closely supervised if any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment: leiomyoma (uterine fibroids) or endometriosis, risk factors for thromboembolic disorders, 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, epilepsy, asthma, otosclerosis. Therapy should be discontinued if a contraindication is discovered and in situations of: jaundice or deterioration in liver function, significant increase in blood pressure or new onset of migraine-type headache. Observational studies show that women prescribed Livial in normal clinical practice, are at an increased risk of having endometrial cancer diagnosed (the 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. If breakthrough bleeding / spotting is still present after 6 months of treatment, starts beyond that time or continues after treatment has been discontinued, women should be advised to report to their doctor. The woman should be referred for gynaecological investigation to exclude endometrial malignancy. Evidence with respect to breast cancer risk in association with tibolone is inconclusive. 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 tibolone therapy is substantially lower than seen in users of oestrogen-progestogen combinations. The level of risk is dependent on duration of use. Ovarian cancer is much rarer than breast cancer. In the Million Women Study, it was shown that the relative risk of ovarian cancer, with tibolone use, was similar to the risk associated with the use of other types of HRT. Oestrogen or oestrogen-progestogen HRT is associated with a 1.3-3 fold risk of developing venous thromboembolism (VTE). The occurrence of such an event is more likely in the first year of HRT than later. Patients with known thrombophilic states have an increased risk of VTE and HRT or tibolone may add to this risk. Generally recognised risk factors for VTE include oestrogen use, older age, major surgery, prolonged immobilization, obesity (BMI > 30 kg/m²), pregnancy/post partum period, systemic lupus erythematosus (SLE) and cancer. As in all postoperative patients, prophylactic measures need to be considered to prevent VTE following surgery. It is recommended to temporarily stop HRT or tibolone 4 to 6 weeks prior to elective surgery if prolonged immobilization is expected. Treatment should not be restarted until the woman is completely mobilised. 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 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, tibolone should be discontinued. Tibolone increases the risk of ischaemic stroke from the first year of treatment, this risk becoming greater with older age. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Livial is not intended for contraceptive use. Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Women with pre-existing hypertriglyceridaemia should be followed closely during treatment. There is some evidence of increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65. The risk of coronary artery disease is slightly
increased in users of combined estrogen-progestogen HRT over the age of 60. There is no
evidence to suggest that the risk of myocardial infarction with tibolone is different to the risk
with other HRT.

**Drug Interactions:** Caution should 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. Since Livial may increase blood fibrinolytic activity,
it may enhance the effect of anticoagulants. An *in vivo* study showed that simultaneous
treatment of tibolone affects pharmacokinetics of the cytochrome P450 3A4 substrate
midazolam to a moderate extent. Drug interactions with other CYP3A4 substrates might
therefore 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 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 LACTATION**
Livial is contraindicated during pregnancy. If pregnancy occurs during medication with
Livial, treatment should be withdrawn immediately. No clinical data on exposed pregnancies
are available. Studies in animals have shown reproductive toxicity. The potential risk for
humans is unknown.

**SIDE EFFECTS**
Refer to SPC for complete information on side effects.
**Common:** Lower abdominal pain, abnormal hair growth, vaginal discharge, endometrial wall
thickening, postmenopausal haemorrhage, breast tenderness, genital pruritus, vaginal
candidiasis, vaginal haemorrhage, pelvic pain, cervical dysplasia, genital discharge,
vulvovaginitis, weight increase and abnormal vaginal smear. **Overdose:** 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.

**Basic NHS Price:** 3 x 28 tablets: £ 31.08   1 x 28 tablets: £ 10.36

**Packaging quantities:** cardboard boxes containing 1 or 3 push through packs of 28 white
tablets.

**Marketing Authorisation Number:** PL 00025/0599

**Legal Category:** POM

**Marketing Authorization Holder:** Merck Sharp & Dohme Ltd., Hertford Road, Hoddesdon,
Hertfordshire, EN11 9BU, UK.

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