AKZO NOBEL

Organon

19th June 2006

IMPORTANT SAFETY INFORMATION

Dear Doctor,

Following discussions with the Irish Medicines Board (IMB), we would like to inform you about updated prescribing advice for Livial (tibolone). The update is the result of the preliminary findings in the Long-term Intervention on Fractures with Tibolone (LIFT) study, in which an increased risk of stroke has been identified.

Updated prescribing advice regarding the risk of stroke

- **Livial is contraindicated in patients with any history of arterial thromboembolic disease, including stroke, TIA, myocardial infarction and angina**

- **Prescribers are warned that a clinical trial of low dose tibolone (1.25mg – currently unlicensed in Ireland) in women (mean age 68 years), has shown an increased risk of stroke compared to placebo after an average of 2.75 years of follow-up. The incidence of strokes observed in the placebo and tibolone arms was 1.8 and 4.1 per 1000 women-years respectively, a difference of approximately 11.5 extra cases per 1000 women over a 5 year period, corresponding to a relative risk of 2.3 (p = 0.02).**

  The absolute risk of stroke identified in this study relates to an older age-group than the typical treatment population for tibolone (for the treatment of menopausal symptoms), however the increased risk was seen with a dose lower than currently licensed. The risk of stroke in currently approved use cannot be directly estimated from these results.

Background – new study data

The LIFT study, a (three-year) placebo-controlled randomised trial examining the effects of 1.25 mg tibolone in the treatment of osteoporosis (unlicensed), was started in 2001. Recruitment was completed in June 2003 with 4,538 subjects. In August 2005, the Data and Safety Monitoring Board (DSMB) reported that more strokes were observed in the tibolone group than in the control group. This was published in the British Medical Journal[1] and communicated to investigators, patients and Health Authorities. In January, 2006, the DSMB reported that this finding persisted, and recommended that the study be stopped earlier than originally planned as the balance of risks and benefits in this trial population was negative.[2]

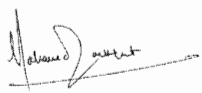
	tibolone	placebo	RR/RH	p value
Stroke (ischemic plus hemorrhagic)	25 (1.11%)	11 (0.49%)	2.3	0.02

Although the data from LIFT are still preliminary, Sections 4.3, 4.4 and 4.8 of the SPC of Livial have been updated (see enclosed SPC).The final study results (expected later this year) will be carefully evaluated and this may result in another update of the SPC.

Organon Laboratories Ltd
Cambridge Science Park
Milton Road
Cambridge CB4 0FL
Tel: (01223) 432700
Telefax: (01223) 424368

Please report suspected serious adverse drug reactions to the company and/or the IMB in the usual way. Should you have any further questions, please contact our medical department at +44 1223 432756.

Yours sincerely,



Mohamed Lockhat
HRT Medical Advisor

[1] Grobbee DE. LIFT study to continue as planned. BMJ 2005;331:843.
[2] Cummings SR. LIFT study is discontinued. BMJ 2006;332:667.

LIVIAL (See SmPC before Prescribing)
Presentation: Calendar pack of 28 Livial tablets, each containing 2.5mg of tibolone. **Uses:** Treatment of oestrogen deficiency symptoms in postmenopausal women. 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. **Dosage and Administration:** 2.5mg Livial orally once daily. HRT should only be continued as long as the benefit in alleviation of severe symptoms outweighs the risk. Not to be taken by women experiencing a natural menopause until 12 months after their last natural menstrual bleed. Changing from another HRT preparation; see SmPC for full details. **Contraindications:** Pregnancy. Lactation. Known, past or suspected breast cancer. Known or suspected estrogen-dependent malignant tumours. Untreated endometrial hyperplasia. Undiagnosed vaginal bleeding. Previous or current VTE. Any history of arterial thromboembolic disease. Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal. Hypersensitivity to any constituents of Livial. Porphyria. **Precautions and warnings:** A full medical history should be taken before treatment. An appraisal of the risks and benefits should be undertaken at least annually. Patients with some medical conditions will need close supervision particularly when the condition is active, or has occurred previously and/or was aggravated during pregnancy or previous hormone treatment - see SmPC for full details of these conditions, which may recur or be aggravated during treatment with Livial. Discontinue treatment if: a contra-indication occurs, jaundice or a deterioration in liver function occurs, there is a significant increase in blood pressure or a new onset of migraine. Break-through bleeding or spotting may occur in the first months of treatment. If bleeding continues during therapy or after discontinuation it should be investigated. For full details on the warnings associated with HRT and endometrial safety, breast cancer, VTE, coronary arterial disease, stroke and ovarian cancer refer to SmPC. Livial tablets contain lactose (See SmPC for details). **Interactions:** No examples of interactions between Livial and other medicines have been reported in clinical practice. The following potential interactions could theoretically occur: Enzyme inducing compounds e.g. barbiturates, carbamazepine, hydantoins and rifampicin may enhance the metabolism of tibolone and decrease its therapeutic effect. Livial may increase blood fibrinolytic activity and may enhance the effect of anticoagulants, such as warfarin. The use of Livial with warfarin should be monitored, especially when starting or stopping concurrent Livial treatment, and the warfarin dose should be appropriately adjusted.
Adverse reactions: The following are the most commonly reported in clinical trials: abdominal pain, weight increase, vaginal bleeding or spotting, leukorrhea, breast pain, genital pruritus, genital moniliasis, vaginitis, hypertrichosis. Other events reported occasionally include; dizziness, rash, seborrhoeic dermatosis, headache, migraine, visual disturbances, GI upset, depression, oedema, effects on the musculoskeletal system and changes in liver function parameters - see SmPC for full details.

Eire
Legal category: Prescription Medicine
Product Authorisation Number: 261/26/1
Package quantities: 1 x 28 tablets
Price: €17.81
Product Authorisation Holder : Organon Laboratories Ltd, Cambridge Science Park, Milton Road, Cambridge, CB4 OFL, UK
Distributor: United Drug PLC

UK
Legal category: POM.
Product Licence Number: PL 0065/0086.
Package quantities: 1 x 28 tablets, 3 x 28 tablets
Basic NHS Cost: 1 x 28 tablets £10.77, 3 x 28 tablets £32.29
Product Licence Holder: Organon Laboratories Ltd, Cambridge Science Park, Milton Road, Cambridge, UK

Further information is available from: Organon Laboratories Limited, Cambridge Science Park, Milton Road, Cambridge, CB4 0FL, UK Telephone: 44 1223 432700.
Date of revision of Prescribing Information: May 2006
Date of preparation: June 2006 Code: 05373B
Help safeguard public health and support medicines yellow card reporting.
UK – see www.yellowcard.gov.uk
Eire – see www.IMB.ie

SUMMARY OF PRODUCT CHARACTERISTICS

RUM1850.061.020
RA 1850 IE S2 (Ref 7)

1. NAME OF THE MEDICINAL PRODUCT

LIVIAL 2.5mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5mg of tibolone.
For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablet
White, round and flat tablets with bevelled edges and a diameter of 6mm 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.

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.

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.
Any irregular/unscheduled vaginal bleeding, either on or off HRT, for which there is no obvious cause, should be investigated before starting Livial (see section 4.3).

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.

Administration
Oral.

4.3 Contraindications

- Pregnancy and lactation
- Known, past or suspected breast cancer
- 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)
- 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, HRT 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 HRT should only be continued as long as the benefit outweighs the risk.

In women with an intact uterus, the risks of breast cancer and 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, 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 hyperplasia and cancer

- Two large UK population-based observational studies, the Million Women Study (MWS) and a General Practice Research Database (GRPD) study, have reported an increased risk of endometrial cancer in women who had used Livial compared with combined HRT and never-users (see section 4.8). The risk increased with increasing duration of use.
- 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.
- The risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone or for prolonged periods. The addition of a progestogen to estrogen-only HRT for at least 12 days per cycle in non-hysterectomised women greatly reduces this risk.

Breast cancer

- A randomized placebo-controlled trial, the Women's Health Initiative study (WHI), and-epidemiological studies, including the Million Women Study (MWS), have reported an increased risk of breast cancer in women taking estrogens, estrogen-progestogen combinations or tibolone for HRT for several years (see section 4.8). For all HRT, an excess risk becomes apparent within a few years of use and increases with duration of intake but returns to baseline within a few (at most five) years after stopping treatment.
- In the MWS, the relative risk of breast cancer with conjugated equine estrogens (CEE) or estradiol (E_2) was greater when a progestogen was added, either sequentially or continuously, and regardless of type of progestogen. There was no evidence of a difference in risk between the different routes of administration. The risk of breast cancer associated with tibolone was lower than the risk associated with estrogen plus progestogen combined HRT, but higher than the risk associated with estrogen-only therapy.
- In the WHI study, the continuous combined conjugated equine estrogen and medroxyprogesterone acetate (CEE + MPA) product used was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases compared to placebo.

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).

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.

Stroke

- One large randomized clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischemic stroke in healthy women during treatment with continuous combined conjugated estrogens and MPA. For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 11 per 1000 women aged 60-69 years. It is estimated that for women who use conjugated estrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate = 1) per 1000 users aged 50-59 years and between 1 and 9 (best estimate = 4) per 1000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products.

- Preliminary results of a randomized double-blind placebo-controlled study (LIFT study, N = 4538) on the efficacy of low dose (1.25 mg) tibolone (N = 2267) for the treatment of osteoporosis in elderly women (mean age 68 years), has shown an increased risk of stroke compared to placebo after an average of 2.75 years of follow-up. The incidence of strokes observed in the placebo and tibolone arms was 1.8 and 4.1 per 1000 women-years respectively, a difference of approximately 11.5 extra cases per 1000 women over a 5 year period, corresponding to a relative risk of 2.3 (p = 0.02).

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 to a different risk than estrogen-only products.

Other conditions

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

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. Therefore, the simultaneous use of Livial and warfarin should be monitored, especially when starting or stopping concurrent Livial treatment, and the warfarin dose should be appropriately adjusted.

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 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 16 placebo-controlled studies, with 1463 women receiving therapeutic doses (1.25 or 2.5mg) of tibolone and 855 women receiving placebo. The duration of treatment in these studies ranged from 2 to 24 months. 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	Abdominal pain	
Metabolic and nutritional disorders	Weight increase	
Reproductive disorders, female	Vaginal bleeding or spotting Leukorrhea Breast pain Genital pruritus Genital moniliasis Vaginitis	
Skin and appendages disorders	Hypertrichosis	
Central and peripheral nervous system disorders		Amnesia

In market use, these undesirable effects were observed as well as some other undesirable effects such as 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. However, in clinical trials, these latter effects were not found to occur statistically significantly more frequently during treatment with tibolone than with placebo.

Breast cancer

According to evidence from a large number of epidemiological studies and one randomized placebo-controlled trial, the Women's Health Initiative (WHI), the overall risk of breast cancer increases with increasing duration of HRT use in current or recent HRT users.
For *estrogen-only* HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which >80% of HRT use was estrogen-only HRT) and from the epidemiological Million Women Study (MWS) are similar at 1.35 (95%CI: 1.21-1.49) and 1.30 (95%CI: 1.21-1.40), respectively.
For *estrogen-progestogen* combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with estrogens alone.
The MWS reported that, compared to 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 tibolone (RR=1.45; 95%CI 1.25-1.68).
The WHI trial reported a risk estimate of 1.24 (95%CI: 1.01-1.54) after 5.6 years of use of estrogen-progestogen combined HRT (CEE + MPA) in all users compared with placebo.
The absolute risks calculated from the MWS and the WHI trial are presented below:
The MWS has estimated, from the known average incidence of breast cancer in developed countries, that:

- For women not using HRT, 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.

The WHI trial estimated that after 5.6 years of follow-up of women between the ages of 50 and 79 years, an *additional* 8 cases of invasive breast cancer would be due to *estrogen-progestogen combined* HRT (CEE + MPA) per 10,000 women years.
According to calculations from the trial data, it is estimated that:

- For 1000 women in the placebo group,
  - about 16 cases of invasive breast cancer would be diagnosed in 5 years.

- For 1000 women who used estrogen-progestogen combined HRT (CEE + MPA), the number of *additional* cases would be,
  - between 0 and 9 (best estimate = 4) for 5 years' use.

The number of additional cases of breast cancer in women who use HRT is broadly similar for women who start HRT irrespective of age at start of use (between the ages of 45-65) (see Section 4.4).

Endometrial cancer

There have been reports of endometrial hyperplasia and endometrial cancer in patients treated with tibolone.
The MWS has estimated an increased risk of endometrial cancer in women who had used Livial compared with never users of HRT (RR approximately 1.8, 95%CI 1.4-2.3). The risk increased with increasing duration of use. The GPRD study has estimated an increase in the risk of endometrial cancer in women who used Livial compared with those who used combined sequential HRT (RR approximately 1.5, 95% CI, 1.0-2.3).

Stroke

The LIFT study has estimated a 2.3-fold increase in the risk of stroke in women (mean age 68 years) who used 1.25 mg tibolone compared with placebo (RR 2.3, p = 0.02). The absolute risk increase is 2.3 strokes per 1000 women treated per year. See section 4.4.

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.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: GO3D C05
After 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 (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.

In vitro studies:
In vitro studies suggest that tibolone exerts tissue-selective effects, due to local metabolism and local effects on enzyme systems. The Δ^4-isomer is mainly formed in endometrial tissue and in the breast, tibolone inhibits the sulfatase enzyme thereby reducing the levels of active estrogens produced in this tissue. The clinical relevance of these studies is not known (see section 4.8).

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.
  - Amenorrhea was seen in 88.4% of the women during months 10-12 of Livial 2.5 mg treatment. Bleeding and/or spotting as captured by means of daily diary cards appeared in 32.6% of the women during the first three months of treatment and in 11.6% during months 10-12 of treatment.
- 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.
  - 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 2 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

2 years

6.4 Special precautions for storage

Do not store above 25°C. Keep the blister in the outer carton.

6.5 Nature and contents of container

The push-through pack is a PVC/Al 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).

6.6 Instructions for use, handling and disposal

No special requirements

7. Marketing Authorisation Holder

Organon Laboratories Limited,
Cambridge Science Park,
Milton Road,
Cambridge,
CB4 0FL,
UK

8. Marketing Authorisation Number

PA 261/26/1

9. Date of First Authorisation/Renewal of Authorisation

9 December 1987/9 December 2002

10. Date of Revision of the Text

May 2006