TIBOFEM Tablets (Tibolone)

Composition

Each uncoated tablet contains:
Tibolone............................. 2.5 mg

Dosage Form

Tablet for oral use

Pharmacology

Pharmacodynamics

Following oral administration, tibolone is rapidly metabolized into three compounds, all of which contribute to its pharmacological effects. Two of these metabolites (3alpha-OH-tibolone and 3beta-OH-tibolone) have oestrogen-like activity, whereas the third metabolite (delta4-isomer of tibolone) has progestogenic and androgenic-like activities.

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

Clinical efficacy and safety

Relief of oestrogen 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 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.

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

In the LIFT study, tibolone reduced the number of women (mean age 68 years) with new vertebral fractures compared to placebo during the 3 years of treatment (ITT: tibolone to placebo odds ratio 0.57; 95% CI). After 2 years of treatment with tibolone (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.

Tibolone (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 tibolone compared to placebo.

Pharmacokinetics

Absorption
Following oral administration, tibolone is rapidly and extensively absorbed. The consumption of food has no significant effects on the extent of absorption.

Metabolism
Due to rapid metabolism the plasma levels of tibolone are very low. The plasma levels of the delta4-isomer of tibolone are also very low. Therefore, some of the pharmacokinetic parameters could not be determined. Peak plasma levels of the 3alpha-OH and the 3beta-OH metabolites are higher, but accumulation does not occur.

<table>
<thead>
<tr>
<th></th>
<th>Tibolone</th>
<th>3alpha-OH Metabolite</th>
<th>3beta-OH Metabolite</th>
<th>Delta4-Isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>1.37</td>
<td>14.23</td>
<td>3.43</td>
<td>0.47</td>
</tr>
<tr>
<td>C&lt;sub&gt;average&lt;/sub&gt;</td>
<td>--</td>
<td>--</td>
<td>1.88</td>
<td>--</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>1.08</td>
<td>1.21</td>
<td>1.37</td>
<td>1.64</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>--</td>
<td>5.78</td>
<td>5.87</td>
<td>--</td>
</tr>
<tr>
<td>C&lt;sub&gt;min&lt;/sub&gt; (ng/ml)</td>
<td>--</td>
<td>--</td>
<td>0.23</td>
<td>--</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-24&lt;/sub&gt; (ng/ml.h)</td>
<td>--</td>
<td>53.23</td>
<td>16.23</td>
<td>--</td>
</tr>
</tbody>
</table>

SD = single dose; MD = multiple dose

Excretion
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.

Special Populations
The pharmacokinetic parameters for tibolone and its metabolites were found to be independent of renal function. No dose adjustment is necessary for the elderly.

Indications
Treatment of oestrogen deficiency symptoms in postmenopausal women, more than 1 year after menopause. 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 TIBOFEM should be based on an assessment of the individual patient’s overall risks and particularly in the age group of over 60 years, should include consideration of the risk of stroke.

Dosage And Administration
The dosage is one tablet (2.5 mg) per day. The tablet should be swallowed with some water or other drink, preferably at the same time of the 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 TIBOFEM treatment.

### Starting Tibofem

Women experiencing a natural menopause should commence treatment with Tibofem at least 12 months after their last natural bleed. In the case of a surgical menopause, treatment with Tibofem may commence immediately. Women being treated with gonadotrophin-releasing hormone (GnRH) analogues, e.g. for endometriosis, may commence treatment with Tibofem immediately.

Any irregular/unscheduled vaginal bleeding, either on or off hormone replacement therapy (HRT), should be investigated to exclude malignancy before starting tibolone.

### Switching from a Sequential or Continuous Combined HRT Preparation

*If changing from a sequential HRT preparation, treatment with Tibofem 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 that 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.

### 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 oestrogen-dependent malignant tumours (e.g. endometrial cancer).
Undiagnosed genital bleeding.
Untreated endometrial hyperplasia.
Previous or current venous thromboembolism (; deep-venous thrombosis, pulmonary embolism).
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 transient ischaemic attack).
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.

### Warnings And Precautions

### General

For the treatment of postmenopausal symptoms, tibolone should only be initiated for symptoms that adversely affect the quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and tibolone should only be continued as long as the benefit outweighs the risk.

The risks of stroke, breast cancer and, in women with an intact uterus, endometrial cancer, 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 breasts) 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. 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 that 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, particularly with tibolone in particular:
- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders
- Risk factors for oestrogen-dependent tumours, e.g. first-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 (SLE)
- A history of endometrial hyperplasia
- 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 tibolone in normal clinical practice are at an increased risk of having endometrial cancer diagnosed. In these studies, the risk increased with increasing duration of use. Tibolone increases endometrial wall thickness, as measured by transvaginal ultrasound.

Breakthrough bleeding and spotting may occur during the first months of treatment. Women should be advised to report any breakthrough 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 a gynaecological investigation, which is likely to include endometrial biopsy to exclude endometrial malignancy.
Breast Cancer
Evidence with respect to breast cancer risk in association with tibolone is inconclusive. The Million Women Study (MWS) has identified a significant increase in the risk of breast cancer in association with use of the 2.5 mg dose. This risk became apparent within a few years of use and increased with duration of intake, returning to baseline within a few years (at the most, 5 years) after stopping treatment. These results could not be confirmed in a study using the General Practice Research Database (GPRD).

Ovarian Cancer
Ovarian cancer is much rarer than breast cancer. Long-term (at least 5-10 years) use of oestrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer. Some studies, including the Women's Health Initiative (WHI) trial, suggest that the long-term use of combined HRTs may confer a similar or slightly smaller risk. In the MWS, 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.

VTE
Oestrogen or oestrogen-progestogen HRT is associated with a 1.3 to 3 fold risk of developing 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. 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.

Generally recognized risk factors for VTE include use of oestrogens, older age, major surgery, prolonged immobilization, obesity (body mass index >30 kg/m²), pregnancy/postpartum period, SLE, and cancer. There is no consensus about the possible role of varicose veins in VTE. As in all post-operative 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 4-6 weeks earlier is recommended, if possible. 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 a 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, 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, dyspnoea).

Coronary Artery Disease (CAD)
There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestogen or oestrogen-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. 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.

Tibolone is not intended for contraceptive use.

Treatment with tibolone results in a marked dose-dependent decrease in HDL-cholesterol (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-cholesterol levels was not dose-dependent. Levels of low-density lipoprotein (LDL)-cholesterol were unchanged. The clinical implication of these findings is not yet known.

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 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 tibolone results in a very minor decrease in thyroid-binding globulin and total T4. Levels of total T3 are unaltered. Tibolone decreases the level of sex-hormone-binding globulin, whereas the levels of corticoid-binding globulin and circulating cortisol are unaffected.

HRT does not improve cognitive function. There is some evidence of an increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65 years.

Drug 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 tibolone and anticoagulants, especially when starting or stopping concurrent tibolone 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 with tibolone affects the pharmacokinetics of the cytochrome (CY) 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 progestogens via CYP3A4. Clinically, an increased metabolism of oestrogens and progestogens may lead to a decreased effect and changes in the uterine bleeding profile.

Pregnancy

Tibolone is contraindicated in pregnancy. If pregnancy occurs during medication with tibolone, treatment should be withdrawn immediately. For tibolone no clinical data on exposed pregnancies are available.

Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Lactation

Tibolone is contraindicated during lactation.

Paediatric Use

There is no relevant use of tibolone in the paediatric population.

Geriatric Use
No dose adjustment is necessary for the elderly.

## Undesirable Effects

The undesirable effects mentioned below were registered in 21 placebo-controlled studies (including the LIFT study), with 4079 women receiving therapeutic doses (1.25 mg 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 1 shows the undesirable effects that occurred statistically significantly more frequently during treatment with tibolone than with placebo.

### Table 1: Undesirable Effects of Tibolone

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common &gt;1%,&lt;10%</th>
<th>Uncommon &gt;0.1%,&lt;1%</th>
<th>Rare &gt;0.1%,&lt;1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Oedema**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Lower abdominal pain</td>
<td>Abdominal discomfort**</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Abnormal hair growth</td>
<td>Acne</td>
<td>Pruritus**</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Vaginal discharge Endometrial wall thickening Postmenopausal haemorrhage Breast tenderness Genital pruritus Vaginal candidiasis Vaginal haemorrhage Pelvic pain Cervical dysplasia Genital discharge Vulvovaginitis</td>
<td>Breast discomfort Fungal infection Vaginal mycosis Nipple pain</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight increase Abnormal cervical smear*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The majority consisted of benign changes. Cervix pathology (cervical carcinoma) was not increased with tibolone compared to placebo.

** These adverse reactions were identified through post-marketing surveillance. The frequency category was estimated based on relevant clinical trials.

In market use, other undesirable effects that have been observed include: dizziness, rash, seborrhoeic dermatosis, headache, migraine, visual disturbances (including blurred vision), depression, effects on the musculoskeletal system such as arthralgia or myalgia, and changes in liver function parameters.

### Breast Cancer

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 the duration of use.
Results of the largest epidemiological study (MWS) are presented below:

Table 2: MWS — Estimated Additional Risk of Breast Cancer after 5 Years of Use

<table>
<thead>
<tr>
<th>Age Range (Years)</th>
<th>Additional Cases per 1,000 Never-Users of HRT over a 5-Year Period</th>
<th>Risk Ratio and 95% CI</th>
<th>Additional Cases per 1,000 HRT Users over 5 Years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oestrogen-only HRT</td>
<td>50–65 &lt;br&gt; 9–12</td>
<td>1.2</td>
<td>1–2 (0–3)</td>
</tr>
<tr>
<td>Combined oestrogen-progestogen</td>
<td>50–65 &lt;br&gt; 9–12</td>
<td>1.7</td>
<td>6 (5–7)</td>
</tr>
<tr>
<td>Tibolone</td>
<td>50–65 &lt;br&gt; 9–12</td>
<td>1.3</td>
<td>3 (0–6)</td>
</tr>
</tbody>
</table>

*Overall risk ratio. The risk ratio is not constant, but will increase with increasing duration of use.

Endometrial Cancer Risk

Postmenopausal Women with a Uterus
The endometrial cancer risk is about 5 in every 1,000 women with a uterus and 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 four cases of endometrial cancer in the tibolone group (n=1,746). This corresponds to a diagnosis of 0.8 additional cases of endometrial cancer in every 1,000 women who used tibolone for 1 year in this study.

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.

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 1.25 mg tibolone (28/2,249) compared with placebo (13/2,257). 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 1,000 women aged 50–59 years, and 11 per 1,000 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 1,000 users aged 50–59 years, and 13 per 1,000 users aged 60–69 years.

Other adverse reactions have been reported in association with oestrogen and oestrogen-progestogen treatment: Long term use of oestrogen-only and combined oestrogen-progestogen HRT has been associated with a slightly increased risk of ovarian cancer. In the MWS, 5 years of HRT resulted in one extra case per 2,500 users. This study showed that the relative risk for ovarian cancer with tibolone was similar to the risk with other types of HRT.

HRT is associated with a 1.3 to 3-fold increased relative risk of developing 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. Results of
the WHI studies are presented:

### Table 3: WHI Studies — Additional Risk of VTE over 5 Years of Use

<table>
<thead>
<tr>
<th>Age Range (Years)</th>
<th>Incidence per 1,000 Women in the Placebo Arm over 5 Years</th>
<th>Risk Ratio and 95% CI</th>
<th>Additional Cases per 1,000 HRT Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral oestrogen-only*</td>
<td>50-59</td>
<td>7</td>
<td>1.2 (0.6–2.4)</td>
</tr>
<tr>
<td>Oral combined oestrogen-progestogen</td>
<td>50-59</td>
<td>4</td>
<td>2.3 (1.2–4.3)</td>
</tr>
</tbody>
</table>

*Study in women with no uterus.

The risk of CAD is slightly increased in users of combined oestrogen-progestogen HRT over the age of 60 years. There is no evidence to suggest that the risk of myocardial infarction with tibolone is different to the risk with other HRT.

### Table 4: WHI Studies Combined — Additional Risk of Ischaemic Stroke over 5 years' use

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Incidence per 1000 women in placebo arm over 5 years</th>
<th>Risk ratio and 95%CI</th>
<th>Additional cases per 1000 HRT users over 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>8</td>
<td>1.3 (1.1 - 1.6)</td>
<td>3 (1 - 5)</td>
</tr>
</tbody>
</table>

Gallbladder disease.

Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura. Probable dementia over the age of 65 years.

**Overdosage**

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

**Storage And Handling Instructions**

Store in a cool, dry place. Protect from light and moisture.

**Packaging Information**

Tibofem is available in a blister pack of 14 tablets.

*Last Updated: Oct 2015*

*Last Reviewed: Oct 2015*

**TIBOFEM Tablets**

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