

**DRUG REVIEW**

Tibolone : A Selective Tissue Estrogenic Activity Regulator

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Tibolone is a STEAR (Selective tissue estrogenic activity regulator) (1). It is a synthetic steroid with tissue selectivity that has progestogenic, some androgenic as well as estrogenic effects. It has been used as an alternative to estrogen replacement therapy in several European countries for almost 2 decades, primarily for the prevention of postmenopausal osteoporosis and treatment of climacteric symptoms.

Mechanism of action (2) : Tibolone itself has no biological activity; its effects are the results of the activity of its metabolites on various tissues. After administration, tibolone is quickly metabolized into 3 α -hydroxytibolone (3 β OH-tibolone) and 3 β -OH-tibolone compounds, which are also present in an inactive, sulfated form. A third compound, the ?4- isomer, is formed from tibolone directly or from the 3 β -OH-metabolites. Tibolone has estrogenic effects on bone and vaginal tissue. In endometrial tissue the ?4-isomer functions as a progestagen, whereas in the brain and liver it has androgenic effects. In breast tissue, the main actions of tibolone are strong inhibition of sulfatase activity and weak inhibition of 17 α -hydroxysteroid dehydrogenase activity, which result in blocking the conversion of estrone sulfate to E2. Tibolone actions are as follows :

Climacteric Symptoms : Menopause-associated symptoms impair quality of life for many women. More than 75% of postmenopausal women experience hot flushes, sweating, insomnia, headache, fatigue, changes in mood and libido. Tibolone has been shown to be effective in the treatment of vasomotor symptoms and provides positive effects on sexual function (3, 4). Tibolone may improve mood, libido and somatic symptoms in surgically menopausal women to a greater extent than estrogen therapy alone (5).

Sexual Function : Tibolone has been shown to increase libido and frequency of sexual activities , mainly by its androgenic activity (6). Clitoral circulation in

postmenopausal women reporting female sexual dysfunction (FSD) is significantly increased under tibolone in comparison with Estrogen progestron therapy with a better improvement of sexual function (7). In the first trial by Neviny-Stickel (8), there was no significant improvement in regard to libido in women taking tibolone. On the contrary, the recent double blind and placebo-controlled trial by Laan (9) has shown that treatment with tibolone significantly improved the physiological aspects of sexual function in postmenopausal women, such as vaginal blood flow, vaginal lubrication, and subjective measures, such as sexual desire and arousability, but there was no difference in the frequency of sexual intercourse, nonpenetrative sexual activity, or initiation and rejection of sexual activity between women who were taking tibolone vs. those receiving placebo (9).

Hot Flushes and Sweating : Compared with placebo, most RCTs reported a significant reduction in hot flushes and sweating in women taking tibolone .When the effects of tibolone on hot flushes were compared with the effects of other hormones, a similar reduction of hot flushes was seen with both therapies. Tibolone and 17 β - oestradiol /dydrogesterone oral tablets were effective and safe to treat short- and intermediate-term symptoms in Middle-Eastern postmenopausal women, within 6 months, and thus, the use of HRT to relieve menopausal symptoms is highly recommended, at least in this region (4). Tibolone induces a significant decrease in the frequency and intensity of climacteric symptoms at a dose levels of 1.25 mg and higher. However, a daily dose of 2.5 mg is the optimal dose (10)

Mood : In one small trial of young women who had undergone oophorectomy and hysterectomy, Crona et al. (11) found that tibolone and E2 valerate reduced hot flushes and improved mood to a similar degree. In another trial, Genazzani (12) found that the relief of hot flushes

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from the second month of treatment was associated with improvement of both mood and insomnia. Tibolone increases the concentration of endorphins which might contribute to the improved mood in postmenopausal women. A Continuous combined hormone replacement regimens, CEE + MPA and tibolone, have superior long-term effects on mood scores in menopause and should be considered during the decision process for use of HRT due to menopausal symptoms (13).

Vaginal Bleeding and Endometrium : In the endometrium, tibolone is transformed into the 7 α - isomer by 3 β -hydroxysteroid dehydrogenase isomerase. This metabolite does not have estrogenic activity, but has intrinsic progestagenic activity; therefore, it does not stimulate the endometrial tissue. Thus, therapy with tibolone may not require the addition of progestagen to protect the endometrium (14). More over, there has been no evidence that tibolone can have adverse effects on the disease free survival and overall survival of endometrial cancer patients. So, tibolone could be used in these patients (15). However, endometrial effects of tibolone need to be assessed in larger trials. A thorough investigation in patients presenting with vaginal bleeding while on tibolone should be carried out, despite the absence of endometrial thickness by sonogram (14)

Lipids : Tibolone decreases triglyceride levels much more than transdermal estradiol. However, HDL cholesterol is decreased by tibolone and increased by transdermal estradiol. Tibolone had a more marked decreasing effect in postmenopausal women who had higher initial triglyceride levels (16). It seems that the beneficial effect of tibolone on the cardiovascular system might be greater in women with a high level of triglycerides whereas hypercholesterolemic women benefit more from the cholesterol-lowering effect of estrogen replacement therapy/HRT (17)

In another study use of tibolone has been suggested to decrease the concentration of the total cholesterol, triglycerides, HDL cholesterol, without a significant decrease of LDL cholesterol. Also, the use of tibolone does not have any significant effect on the concentrations of antitrombin III, fibrinogen and C-reactive protein (18). However, the androgenic effects of tibolone can increase fibrinolytic activities (19) which can be cardioprotective.

Breast Cancer : There is clear evidence that HRT causes breast cancer and the challenge for the physician is to control the menopausal symptoms using HRT or

alternatives while at the same time limiting the risks associated with this treatment. Tibolone, a gonadomimetic agent which has been used to control menopausal symptoms, appears to have less direct effects on the breast (20). In breast cells, tibolone slows down the proliferation rate as well as increases differentiation and apoptosis. This has led to the view that tibolone might reduce breast cancer risk.(21). Colacurci showed that 1 yr of tibolone treatment did not affect breast density in postmenopausal women with normal breast tissue compared with a control group and a hormonal replacement therapy group (22). Hammar (23) reported that postmenopausal women taking tibolone experienced breast tenderness significantly less frequently than those who were taking E2/NETA.

Epithelial Ovarian Cancer : There is no evidence that tibolone can have detrimental effects on the progression free survival and overall survival of epithelial ovarian cancer patients. So, tibolone can be used in these patients (24).

Postmenopausal Osteoporosis (25,26) : Tibolone prevents bone loss in a similar way to estrogens. Loss of bone in the spine and proximal hip can be prevented with tibolone 2.5 mg/day in early and late postmenopausal women. Many studies show increase in bone mineral density at other sites like phalanges and hip. Tibolone is effective, even at lower doses, in preventing a decrease in spine and femur BMD in early postmenopausal women(25). Tibolone might be such an agent. However, so far, no fracture data are available; all existing studies have shown a positive action of tibolone on bone mineral density. No study has been tailored to study the antifracture efficacy. The Long Term Intervention on Fractures with Tibolone (LIFT) study has been started with the aim at filling the gap between bone mineral density maintenance and bone fracture prevention(26).

Current recommendation : An international multidisciplinary panel of experts met at the 4th Amsterdam Menopause Symposium in October 2004 and the consensus was that tibolone is a valuable treatment option for women with climacteric complaints (27). It has positive effects on sexual well-being and mood, and improves vaginal atrophy and urogenital symptoms. Absolute numbers of women at increased risk for breast cancer are estimated to be low or absent with both tibolone and ET, and the risk with tibolone should be significantly lower than that with EPT. Tibolone might therefore be preferable to EPT in certain women who have not been hysterectomised (27).