AUSTRALASIAN MENOPAUSE SOCIETY
EMPOWERING MENOPAUSAL WOMEN

Information Sheet

Tibolone as menopausal hormone therapy

Key Points

- Tibolone acts as a combined oral hormone therapy for treating menopausal symptoms
- It has not been researched as extensively as some other forms of HT
- Evidence for improved sexual function with tibolone is not strong
- An increased risk of stroke was found in women over 60 years of age
- It is contraindicated in women who have had breast cancer
- Risks vs benefits for an individual need to take into account their co-morbidities.

What is tibolone?

Tibolone is a synthetic steroid molecule which is, in essence, a progestogen. Post absorption, its metabolites have oestrogenic, progestogenic and androgenic properties (1, 2). The oestrogenic effects are exerted mainly in brain, bone and vaginal tissues and are responsible for control of vasomotor symptoms and prevention of bone loss. The effect of the progestogenic metabolites on the endometrium prevents hyperplasia. Limited conversion of oestrone to oestradiol may reduce the oestrogenic effects of tibolone in the breast. Androgenic effects are thought to enhance testosterone availability by reducing sex hormone binding globulin (SHBG).

How effective is tibolone?

In randomized trials tibolone 2.5mg has been found to be more effective than placebo and less effective than standard dose combined MHT in controlling vasomotor symptoms. Moderate-quality evidence also suggests that tibolone is associated with a higher rate of unscheduled bleeding than placebo, but a lower rate of bleeding than with combined MHT (2).

Tibolone has been found to be effective in the prevention of bone loss. The effect of tibolone on bone seems similar to MHT (3). In the LIFT study the absolute reduction in vertebral fractures in the tibolone group, was 8.6 (95% CI, 4.4 to 12.9) per 1000 person-years with a relative reduction hazard of 45% (95% CI, 26 to 59) (4). There was also a reduction in the absolute risk of nonvertebral fracture. Adverse events seen in the LIFT study limit its usefulness for the older population with low bone density.

Tibolone decreases SHBG and increases bioavailable testosterone. In addition, the Δ4-isomer of tibolone stimulates androgen receptors. Both of these actions are thought to have a positive effect on sexual function. However, there is low quality evidence for this. A Cochrane meta-analysis of studies of tibolone v placebo in postmenopausal women found no effect to a small benefit, with wide confidence intervals (5).

Randomized controlled trials have studied tibolone v MHT for sexual function. Two large trials have studied tibolone v transdermal MHT. The LISA study randomised 403 women to tibolone or transdermal oestradiol/norethisterone for 24 weeks (6). Both treatments found improvement in the satisfying sexual event rate for both groups, with no difference between groups. In the per protocol analysis, but not in the intent-to-treat analysis, the increase in Female Sexual Function Index (FSFI) scores was significantly greater in the tibolone group when compared with the MHT group ($p = 0.025$). A 48-week study of 437 women randomized to tibolone or transdermal oestradiol/norethisterone found improvement in both groups on McCoy's Sex Scale Questionnaire (7).

Other studies compared tibolone with oral MHT. A study comparing tibolone, oral CEE/MPA and placebo found a significant increase in sexual function, as measured by the FSFI, in the tibolone group but no statistically significant difference between tibolone and CEE/MPA (8). Uygur et al found improved sexual function in tibolone v CEE/MPA in face-to-face questioning rather than a standardised questionnaire (9).

Who can use tibolone?

Tibolone can be used by women who have an intact uterus and have not experienced a natural period for at least one year. If taken sooner, irregular bleeding may be experienced. Women can also transition from cyclical, or combined continuous MHT onto Tibolone. Tibolone has the same contraindications as any oral combined MHT.

Side-effects of tibolone

Side-effects may include headache, dizziness, nausea, abdominal pain, swollen feet and itching. Breast tenderness is uncommon. Slight bleeding or spotting may commonly occur initially but tends to subside after a few months. Amenorrhoea is achieved by about 80% of women after the first month of treatment with tibolone and over 90% after the third month of therapy (10).

Safety of tibolone

- In the LIFT study of tibolone for the prevention of bone loss and osteoporotic fractures, there was an increase in stroke in the tibolone group compared with the placebo group (4). This was mainly seen in women over 60 years of age. The increase among women in their 50s was 4 extra cases per 1000 and among women in their 60s, an extra 13 cases per 1000 women.
- Tibolone decreases total and LDL cholesterol and triglyceride levels. However, it also decreases HDL cholesterol. The impact of these changes on cardiovascular events is not clear. Meta-analysis of only four studies examining this showed a non-significant odds ratio for cardiovascular events with tibolone of 1.38 [0.84, 2.27] (2).
- The data on breast safety have been contradictory. Preclinical data on tibolone concentrated on its effect on oestrogen metabolism in the breast. Tibolone and its metabolites reduce sulfatase and stimulate sulfotransferase activity thereby inhibiting the formation of active

oestrogenic substances and promoting the formation of inactive oestrogens (11). It is associated with less breast density than conventional continuous combined MHT (12). It was therefore thought to be safer, in terms of breast cancer risk, for women at risk of breast cancer or even those who had had breast cancer. However, in the LIBERATE study tibolone was found to increase the risk of recurrence of breast cancer in patient with treated breast cancer with an odds ratio of 1.50 (1.21, 1.85) (13).

There are very few randomized trials of tibolone in women without breast cancer history with breast cancer as a secondary endpoint. A meta-analysis of four studies showed no significant increase in breast cancer (2).

However, there are epidemiological studies which raise concern. The Million Women Study, an uncontrolled study based on recall of MHT use, reported an increase in breast cancer with tibolone use - 1·45 (1·25–1·68), p<0·0001. An Australian case-control study found an odds ratio of 2.27 (1.01-5.10) for current tibolone use (14). A data linkage study from Norway identified a relative risk of 1.91 (1.61-2.28) in tibolone users (15). A prospective data-linkage study in Sweden also reported an increase in odds ratio with tibolone use of 1.68 (1.51-1.87) (16).

- In addition, a data-linkage study from Denmark identified current users of tibolone had an increased relative risk for ovarian cancer of 1.42(95% CI, 1.01–2.00) and serous ovarian tumors of 2.21 (95%CI 1.48–3.32)). Compared to never users, the relative risk of endometrial cancer was 3.56 (95%CI 2.94–4.32) among current users of tibolone and 3.80 (95%CI 3.08–4.69) of type 1 endometrial cancer (17).

It is not clear why the preclinical data and the epidemiological studies are at such variance. It is possible that there may be some ascertainment bias, in that women with an increased risk of breast cancer were prescribed tibolone in preference to conventional MHT. It is also possible that the reassuring oestrogen metabolism data for tibolone has overlooked the contribution of progestogen to breast cancer risk, as was identified in the WHI study.

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