AUSTRALASIAN MENOPAUSE SOCIETY
EMPOWERING MENOPAUSAL WOMEN

Information Sheet

Tibolone as menopausal hormone therapy

Key Points

- Tibolone is a synthetic steroid hormone. Its metabolites have oestrogenic, progestogenic and androgenic properties
- Tibolone is indicated for the management of oestrogen deficiency symptoms and for the prevention of bone loss at the time of menopause
- Some studies have reported an improvement in sexual function or libido with the use of tibolone
- Tibolone is not recommended for use in women with a history of breast cancer and should be used with caution in women over age 60.

What is tibolone?

Tibolone is a synthetic steroid which has oestrogenic, progestogenic and androgenic action. The drug is metabolised into three active metabolites, two of which bind solely to the oestrogen receptor, and a third which has affinity for the progesterone (preventing endometrial hyperplasia) and androgen receptors. The oestrogenic effects are exerted mainly in bone and vagina and are responsible for control of vasomotor symptoms and prevention of bone loss. In limiting the conversion of oestrone to oestradiol, tibolone may reduce the oestrogenic effects in breast tissue. Tibolone has androgenic effects in the brain and liver; both by reducing SHBG and by weak stimulation of the androgen receptor. (1, 2)

How effective is tibolone?

Vasomotor symptoms: Evidence from randomised trials suggests that tibolone 2.5mg is more effective than placebo but less effective than combined MHT in controlling vasomotor symptoms. Tibolone is associated with a higher rate of unscheduled bleeding than placebo but a lower rate than combined MHT (3).

Bone health: The effect of tibolone on preventing bone loss is similar to MHT (4). In the LIFT study, 4538 women age 60-85 years with osteoporosis on the basis of BMD or minimal trauma vertebral fracture, were randomised to 1.25mg tibolone or placebo. After a median of 34 months, there was a significant reduction in the absolute risk of

both vertebral and non-vertebral fractures. The reduction in fracture risk was also seen in women with a pre-existing vertebral fracture.

Sexual health: Tibolone improves sexual function in women with low libido, compared to placebo in clinical trials, which may be due to tibolone's combined oestrogenic and androgenic properties. (5, 6) . Whether there is any advantage of tibolone compared to conventional MHT is unclear with studies yielding both positive and negative outcomes (7-9) .

Who can use it?

Tibolone can be used by post-menopausal women who have an intact uterus and have not experienced a natural period for at least one year. If taken sooner, in the perimenopause, 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

Side effects of tibolone 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).

Long term safety of Tibolone

Evidence to assess the long-term safety of tibolone compared to placebo or MHT is limited as most studies provide follow-up for only two to three years. Compared to placebo, tibolone appears to increase the risk of recurrence in women with a history of breast cancer and may increase the risk of stroke in women over 60 years of age.

Breast: Preclinical studies looked at the effect of tibolone on oestrogen metabolism in the breast and in breast cancer cells. As it slowed proliferation and increased apoptosis in the breast cancers it was thought to be safer for women at risk of or who had a history of breast cancer. In a small clinical trial it was associated with less mammographic breast density, compared to combined MHT and no different to placebo after six months (11). While there are very few randomized trials of tibolone in women without a history of breast cancer with breast cancer as a secondary endpoint, a systematic review of four studies showed no significant increase in breast cancer (3). In contrast, epidemiological studies including the Million Women Study, reported an increase in breast cancer among current users of MHT including tibolone (12-15), and the LIBERATE study reported *increased* recurrence of breast cancer in patients taking tibolone (16). It is therefore currently recommended that women with a history of breast cancer should not be prescribed tibolone (17).

Cerebrovascular events: The LIFT study demonstrated an increase in stroke in the tibolone group compared with the placebo (18). Like other hormone treatments the risk was greatest in the first year of use and the risk increased with age. For women aged 60 – 69 the absolute risk was 2.8 times greater than the placebo group. Conversely, the Cochrane systematic review which included 4 RCT's, showed no increase in stroke rate with tibolone use (3).

Cardiovascular disease and Lipids

Of the few RCT's that compare tibolone vs placebo or MHT, no significant difference has been demonstrated in cardiovascular events. Similarly, the Cochrane systematic review demonstrated no difference in the incidence of venous thromboembolic events between the tibolone and placebo group. A systematic review and meta-analysis (19) concluded tibolone decreased total cholesterol, HDL and triglycerides.

Endometrial Malignancy

A Danish registry study found an increased risk of endometrial malignancy in Tibolone users compared to non-users (20). Importantly though, the Cochrane systematic review which included 8 randomised controlled trials comparing Tibolone with placebo, did not show any difference between the two groups (3). There were however, low case number reported in both groups and follow up only to 3 years. It is recommended that women taking Tibolone who experience unexpected post-menopausal bleeding undergo investigation as for women who take conventional MHT.

Summary

Tibolone is indicated for the management of vasomotor symptoms associated with the menopause and for the prevention of bone loss. It can be considered an alternative to conventional MHT where improvement in libido is desired. Its effect on lipid metabolism and haemostasis are less certain, while the long-term effects of tibolone on breast cancer and cardiovascular disease remain unknown. It is not recommended for use in women with a history of breast cancer and should be used with caution in women over age 60 because of the increased stroke risk.

References:

1. Kloosterboer HJ. Tibolone: a steroid with a tissue-specific mode of action. J Steroid Biochem Mol Biol. 2001;76(1-5):231-8.
2. Modelska K, Cummings S. Tibolone for postmenopausal women: systematic review of randomized trials. J Clin Endocrinol Metab. 2002;87(1):16-23.
3. Formoso G, Perrone E, Maltoni S, Balduzzi S, Wilkinson J, Basevi V, et al. Short-term and long-term effects of tibolone in postmenopausal women. Cochrane Database Syst Rev. 2016;10(10):CD008536.
4. Berning B, Bennink HJ, Fauser BC. Tibolone and its effects on bone: a review. Climacteric. 2001;4(2):120-36.

5. Hudita D, Posea C, Ceausu I, Rusu M. Efficacy and safety of oral tibolone 1.25 or 2.5 mg/day vs. placebo in postmenopausal women. Eur Rev Med Pharmacol Sci. 2003;7(5):117-25.
6. Laan E, van Lunsen RH, Everaerd W. The effects of tibolone on vaginal blood flow, sexual desire and arousability in postmenopausal women. Climacteric. 2001;4(1):28-41.
7. Nathorst-Boos J, Hammar M. Effect on sexual life--a comparison between tibolone and a continuous estradiol-norethisterone acetate regimen. Maturitas. 1997;26(1):15-20.
8. Ziaei S, Moghasemi M, Faghihzadeh S. Comparative effects of conventional hormone replacement therapy and tibolone on climacteric symptoms and sexual dysfunction in postmenopausal women. Climacteric. 2010;13(2):147-56.
9. Uygur D, Yesildaglar N, Erkaya S. Effect on sexual life--a comparison between tibolone and continuous combined conjugated equine estrogens and medroxyprogesterone acetate. Gynecol Endocrinol. 2005;20(4):209-12.
10. Hammar M, Christau S, Nathorst-Boos J, Rud T, Garre K. A double-blind, randomised trial comparing the effects of tibolone and continuous combined hormone replacement therapy in postmenopausal women with menopausal symptoms. Br J Obstet Gynaecol. 1998;105(8):904-11.
11. Lundstrom E, Christow A, Kersemaekers W, Svane G, Azavedo E, Soderqvist G, et al. Effects of tibolone and continuous combined hormone replacement therapy on mammographic breast density. Am J Obstet Gynecol. 2002;186(4):717-22.
12. Beral V, Reeves G, Bull D, Green J, Million Women Study C. Breast cancer risk in relation to the interval between menopause and starting hormone therapy. J Natl Cancer Inst. 2011;103(4):296-305.
13. Salagame U, Banks E, Sitas F, Canfell K. Menopausal hormone therapy use and breast cancer risk in Australia: Findings from the New South Wales Cancer, Lifestyle and Evaluation of Risk study. Int J Cancer. 2016;138(8):1905-14.
14. Roman M, Sakshaug S, Graff-Iversen S, Vangen S, Weiderpass E, Ursin G, et al. Postmenopausal hormone therapy and the risk of breast cancer in Norway. Int J Cancer. 2016;138(3):584-93.
15. Brusselaers N, Tamimi RM, Konings P, Rosner B, Adami HO, Lagergren J. Different menopausal hormone regimens and risk of breast cancer. Ann Oncol. 2018;29(8):1771-6.
16. Kenemans P, Bundred NJ, Foidart JM, Kubista E, von Schoultz B, Sismondi P, et al. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. Lancet Oncol. 2009;10(2):135-46.
17. Santen RJ, Stuenkel CA, Davis SR, Pinkerton JV, Gompel A, Lumsden MA. Managing Menopausal Symptoms and Associated Clinical Issues in Breast Cancer Survivors. J Clin Endocrinol Metab. 2017;102(10):3647-61.
18. Cummings SR, Ettinger B, Delmas PD, Kenemans P, Stathopoulos V, Verweij P, et al. The effects of tibolone in older postmenopausal women. N Engl J Med. 2008;359(7):697-708.
19. Lv C, Zhang W, Tan X, Shang X, Gaman MA, Salem H, et al. The effect of tibolone treatment on lipid profile in women: A systematic review and dose-response meta-analysis of randomized controlled trials. Pharmacol Res. 2021;169:105612.
20. Lokkegaard ECL, Morch LS. Tibolone and risk of gynecological hormone sensitive cancer. Int J Cancer. 2018;142(12):2435-40.