IRISH MEDICINES BOARD

Notice Information: - 3rd Party Publications 04 May 2009

Part 1. Product Information

a)	Title:	Tibolone and Breast Cancer – Result of LIBERATE trial – May 09, 2009 - MIMS Publication
b)	Product Name/Type:	Tibolone
c)	Reference:	MIMS Publication

Part 2. Problem/Issue

a) Problem/Issue:

Tibolone (Livial) is a synthetic hormone therapy that is licensed as a first-line treatment for menopausal symptoms and a second-line therapy for prevention of osteoporosis in postmenopausal women who are at high risk of future fracture.

There are limited clinical trial data and conflicting epidemiological evidence regarding the risk of breast cancer associated with tibolone use1,2. This article provides a summary of the findings of the recent LIBERATE study. The primary objective of this trial was to investigate safety of tibolone 2.5mg in women with climacteric symptoms who had been surgically treated for primary breast cancer within the past five years. The aim was to demonstrate that tibolone was non-inferior to placebo regarding breast cancer recurrence rate. Formally, non-inferiority versus placebo could not be shown, which supports the current contraindication of a history of breast cancer.

Tibolone and breast cancer

LIBERATE trial ^{3, 4} <sup>

</sup>The LIBERATE trial was designed to investigate whether tibolone is effective and safe to use in women with a history of breast cancer. This multicentre, randomised, double-blind, placebo-controlled trial recruited women who had had surgery for primary breast cancer within the last 5 years (n=1579 in tibolone group and 1569 in placebo group). The study was stopped early because it identified a significantly increased frequency of breast cancer recurrence in the tibolone group compared with the placebo group (237 vs. 165 cases, respectively, hazard ratio 1•4 [95% CI 1•1–1•7]). The trial also confirmed a higher incidence of vaginal bleeding or spotting and increased endometrial thickness in the tibolone group compared with placebo.

Formally, non-inferiority versus placebo could not be shown, which supported the contraindication of a history of breast cancer. However, not only the upper limit of the 95% CI of 1.789, but also the point estimate (HR) of the difference between placebo and tibolone 1.40 (ITT) exceed largely the pre-defined non-inferiority margin of 1.278, indicating an increased risk of breast cancer during use with tibolone in women with a history of breast cancer. This new data confirm the observation from the observational Million Women Study, which reported a 1.5 fold increased risk of breast cancer in HRT therapy with tibolone compared to non-users of HRT. Advice for Healthcare Professionals:

Advice for Healthcare Professionals:

Tibolone (or conventional HRT) should not be used in women with known or suspected breast cancer, or in those with a history of breast cancer. The prescribing information is presently being updated to include a warning that tibolone increased the risk of breast cancer recurrence in a placebo-controlled trial.

1. Million Women's Steering Committee. Lancet 2003; 362: 419–27.

2.Opatrny L, et al. BJOG 2008; 115: 169–75

3. Kenemans P, et al. Breast 2007; 16 (suppl 2): S182–89.

4.Kenemans P, Bundred NJ, Foidart JM, Kubista E, von Schoultz B, Sismondi P, Vassilopoulou-Sellin R, Har Yip C, Egberts J, Mol-Arts M, Mulder R, van Os S, Beckmann MW, on behalf of the LIBERATE Study Group* Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. Lancet Oncology 2009; 10: 135–46.