a greater decrease in triglycerides.[96] Assessment of pre- and post-menopausal women before and after tibolone treatment for three months revealed a lowering of BP, glucose, TNF-α and HDLC relative to no treatment. Although tibolone was able to reverse some of the common biochemical markers in menopausal women associated with increased CVD risk, the HDLC reduction is a disadvantage.[97] The effects on actual CVD risk reduction and the incidence of cardiac events for women on tibolone await the outcome of large-scale trials or epidemiological studies. Stroke incidence with tibolone is unresolved with some studies reporting an increased incidence[98] and others not.[99]

Significant interactions (tibolone)

Hepatic enzyme inducers such as barbiturates, phenytoin sodium, carbamazepine and rifampicin may accelerate tibolone metabolism. Tibolone can increase the anticoagulant effect of warfarin. *Hypericum perforatum* has also been observed to interact with tibolone[100] (see below).

Risks and unwanted effects (tibolone)

Side effects of tibolone therapy are reported as depression and mood change, weight gain, oedema, dizziness, headaches and migraine, visual disturbances, gastrointestinal symptoms and abnormal liver function tests. Facial hair growth may occur as a result of the androgenicity of the medication.

A multicentre trial was conducted in 31 countries to assess the outcome of tibolone use by breast cancer patients with menopausal symptoms in terms of risk of cancer recurrence. Women who had undergone surgical treatment for breast cancer were randomly assigned to tibolone 2.5 mg daily or placebo. The primary end-point was breast cancer recurrence, including contralateral breast cancer. At the beginning of the study entry, 67 per cent of the women used tamoxifen and 6.5 per cent were taking aromatase inhibitors. At follow-up at a median of 3.1 years, 15.2 per cent of the women on tibolone had a cancer recurrence compared with 10.7 per cent on placebo. Tibolone was similar to placebo with regard to other safety outcomes, such as mortality, cardiovascular events and gynaecological cancers. Vasomotor symptoms and BMD improved significantly with tibolone compared with placebo.[101] In some trials healthy women using tibolone have not been shown to have increased breast cancer risk,[102] however, the consensus from a critical review of the literature is in favour of a lack of convincing data for safety in terms of breast cancer risk.[103]

A single case is reported of a woman on tibolone therapy for two years who developed acute hepatitis, cholestasis and aspects of vanishing bile duct syndrome after ten weeks of *Hypericum perforatum* infusions. The liver injury was attributed to a herb–drug reaction, and although caution is warranted, a number of patients have been observed on the same combination without ill effect.[104]

Benefits other than primary indication (tibolone)

This form of HT is prescribed to women with low libido because it possesses mild androgenicity.[105] Improvements in vaginal dryness, dyspareunia, sexual enjoyment and libido were demonstrated in one study.[106]

Selective oestrogen-receptor modulators (SERMs)

Selective oestrogen-receptor modulators such as raloxifene (Evista) and tamoxifen (Genox, Nolvadex, and Tamoxen) are compounds that have oestrogen agonist activity at some sites and antagonist activity at others. For example, tamoxifen and raloxifene both exhibit antagonistic (antioestrogenic) activity in the breast and agonistic activity in bone and on lipids, but only tamoxifen has agonistic activity in the uterus.

These SERMs effects are mediated via their ability to activate oestrogen receptor -alpha (ER-α) and oestrogen receptor -beta (ER-β). These two receptors are coded by different genes and their tissue expression varies across organs. Oestrogen receptor -α is predominantly expressed in reproductive tissues (uterus, breast, ovaries), liver and the central nervous system, whereas ER-β is expressed in other tissues such as bone, endothelium, lungs, urogenital tract, ovaries and the central nervous system. When tamoxifen and raloxifene were tested in an endometrial cancer cell line, tamoxifen activated 17 regions with ER-α, whereas raloxifene activated only two regions, which likely explains their different effects on the endometrium. Additionally, the ability of raloxifene to activate over twice as many regions with ER-β compared to ER-α explains the positive effects in bone in postmenopausal women and the lack of adverse effects in the breast and endometrium.[107]

Tamoxifen (Genox, Nolvadex, Tamoxen)

Tamoxifen is a first generation SERM with both oestrogenic and antioestrogenic effects, which is used as a breast cancer prophylactic agent. As already described, tamoxifen has antioestrogenic action on

breast tissue but oestrogenic actions on plasma lipids, endometrium and bone in post-menopausal women. It produces mild oestrogen-like adverse effects consistent with partial agonist activity. In breast tissue, tamoxifen competes for endogenous oestrogen for ERs and therefore inhibits the transcription of oestrogen-responsive genes. As a result, the growth of tumours is slowed or even halted.[108]

Placebo controlled trials in over 25 000 women examining the prophylactic use of tamoxifen demonstrated a significant reduction in ER positive (ER+) breast cancer occurrence by about 40 per cent.[109] This is evident in women across all ages with a reduced risk of primary, secondary, and/or contralateral breast cancer.[110] Tamoxifen is prescribed as an antioestrogen at doses of between 20–40 mg, when women have ER+ breast cancer to lower the risk of recurrence or relapse of ER+ tumours. Tamoxifen is also indicated for the management of metastatic disease associated with breast cancer. Metastases of the skin, nodes and bone respond better to tamoxifen than cancers in organs such as the lung. More recently, comparisons between aromatase inhibitors and tamoxifen have shown more favourable results with the former class of medication, and tamoxifen therapy is no longer considered 'gold standard' adjuvant therapy for early breast cancer.[111]

Raloxifene (Evista)

Raloxifene was initially used as a medication for enhancing bone density in osteoporosis, however, its actions were found to be similar to tamoxifen in decreasing the risk of breast cancer recurrence. Placebo-controlled trials in nearly 18 000 women have shown that raloxifene reduces breast cancer risk by between 44–72 per cent.[112] Unlike tamoxifen, raloxifene does not increase endometrial cancer risk. In keeping with its SERM effects, raloxifene shares the benefits of oestrogen on bone, but does not exert the adverse effects on the breast and endometrium. Similarly, like oestrogen, raloxifene decreases bone turnover by inhibiting reabsorption. In terms of lipids, it lowers total cholesterol and LDLC, has no impact on HDLC and, unlike oestrogen therapy, does not increase triglycerides.[113]

Significant interactions (SERMs)

The effectiveness of tamoxifen is related to the ability of the hepatic enzyme CYP 2D6 (CYP2D6) to metabolise tamoxifen to endoxifen, the metabolite thought to be responsible for beneficial effects of tamoxifen in breast cancer patients and those at high risk for breast cancer. Women with impaired CYP2D6 metabolism have been observed to have lower endoxifen concentrations and a higher risk of breast cancer progression. A wide range of medications can inhibit CYP2D6 and include:

- *some selective serotonin re-uptake inhibitors (SSRIs) or selective noradrenergic re-uptake inhibitors (SNRIs)*:
  - paroxetine, fluoxetine, bupropion and duloxetine
- *antipsychotic medications*:
  - thioridazine, perphenazine and pimozide
- *cardiac drugs*:
  - quinidine and ticlopidine
- *some medications used in infectious disease treatment*:
  - terbinafine and quinidine
- *the calcimimetic*:
  - cinacalcet hydrochloride.

Alternative medications should be chosen from within each drug class for women on tamoxifen that exhibit lower levels of CYP2D6 inhibition.[114]

A Canadian study examined the effect of SSRIs which inhibit CYP2D6 by reviewing the medical records of 2430 female breast cancer survivors, approximately 30 per cent of whom had an overlapping treatment period with a single SSRI. Absolute increases in the risk of death from breast cancer paralleled the duration of administration of tamoxifen with overlapping use of paroxetine, such that longer duration of use was associated with an increase in the number of cancer-related deaths. Paroxetine is an irreversible inhibitor of CYP2D6 and appears to abolish or reduce the beneficial effects of tamoxifen in terms of breast cancer survival. No association was observed for other antidepressants such as citalopram and venlafaxine. The authors concluded that other SSRIs not studied which also inhibit CYP2D6, such as fluoxetine, should probably also be avoided.[115]

A phase II study examined the concomitant use of melatonin with tamoxifen in women with metastatic breast cancer who had experienced disease progression on tamoxifen alone. The combination treatment consisted of tamoxifen 20 mg daily at noon and melatonin 20 mg daily in the evening and resulted in tumour regression and a decrease in insulin-like growth factor 1 (IGF-1) in metastatic breast cancer patients refractory to tamoxifen treatment alone.[116]

Following chemotherapy, pre-menopausal women typically experience amenorrhoea of unknown duration. This, combined with tamoxifen, can give rise to moderate to severe hot flushes and other adverse menopausal symptoms for which women may request symptom relief or treatment to reinstate their menstrual cycle. However, since candidates for tamoxifen have ER+ breast cancers, herbs which can potentially improve ovulation and menstrual cycle regularity should be avoided on the basis that the higher oestrogen levels associated with ovulatory cycles are disadvantageous for these women. *Vitex agnus-castus* should thus be used very cautiously or not at all for women with menopausal symptoms. On the other hand, preliminary studies on *Actea/Cimicifuga racemosa* indicate a potentially beneficial outcome can be obtained by co-administration with tamoxifen in terms of symptom reduction and improved disease-free interval (see page 840 for further discussion). Because of this, the most common referral from a gynaecological oncologist to the clinic is for the management of women with tamoxifen-induced menopausal symptoms with *Actea/Cimicifuga racemosa.*

Although vitamin E has been shown to inhibit ER+ cell growth *in vitro*, this effect is not apparent when women are taking tamoxifen.[117] In a small study of seven women on tamoxifen therapy, concurrent administration of vitamin E led to lowered tamoxifen levels in five of seven of the women, with four of these women having subtherapeutic tamoxifen levels. In addition, oestrogen stimulation biomarkers (including ER and progesterone receptor) were higher in breast biopsies of women taking vitamin E with tamoxifen, indicating that vitamin E should be avoided on the basis that it appears to interfere with the therapeutic effects.[118]

Risks and unwanted effects (SERMs)

The unwanted effects of tamoxifen and raloxifene include hot flushes, menstrual irregularity, nausea, headaches, fluid retention and vaginal dryness or irritation. Venous thrombosis, stroke and pulmonary embolus risk increase with both drugs and thus they are not recommended for women with significant risk or a history of these events.[119] Tamoxifen use has been associated with an increase in endometrial hyperplasia, polyps and cancer, and caution is warranted for women with co-morbidities, including a prior history of endometrial hyperplasia or obesity.

Benefits other than primary indication (SERMs)

Studies of post-menopausal women with early stage breast cancer taking tamoxifen in 1992[120] and again in 2004[121] showed a modest BMD increase and a significant osteocalcin decrease when compared to placebo that is consistent with an oestrogen-like effect on bone turnover. Raloxifene has superior bone enhancing effects to tamoxifen, although less than bisphosphonates or oestrogen. An increase in bone density by approximately 2–3 per cent for both spine and hip was observed after 2–3 years of raloxifene therapy.[122] In terms of fracture prevention, raloxifene given over three years decreased vertebral fracture risk by 30–50 per cent in post-menopausal women with osteoporosis.[123] The decreased risk was marginally better in women taking 120 mg daily compared to the standard 60 mg daily dose.

Nutrients, foods and herbs (SERMs)

A number of nutrients and food compounds appear to be advantageous for women taking tamoxifen. Synergistic inhibition of tumour growth and an increase in apoptosis were observed in ER+ breast cancer xenografts when tamoxifen and methylselenocysteine were combined.[124] Pterostilbene, a bioavailable stilbenoid found in blueberries, combined with tamoxifen *in vitro* with breast cancer cell lines showed additive reductions in cell viability and increased apoptosis, suggesting that eating blueberries while on tamoxifen may be advantageous.[125] Women taking tamoxifen were shown to have lower levels of the carotenoids lycopene, alpha-carotene and betacarotene, suggesting supplements or dietary adjustment is necessary.[126] Concurrent administration of 100 mg coenzyme Q10 (CoQ10), 10 mg riboflavin and 50 mg niacin with tamoxifen 10 mg twice daily significantly reduced tumour markers cancer antigen 15-3 (CA 15-3) and serum carcinoembryonic antigen (CEA) levels. This may indicate a reduced risk of developing metastases.[127]

A number of investigators have established a beneficial effect from combining flaxseed or flaxseed oil with tamoxifen therapy.[128] An animal study was devised in order to elucidate which component of flaxseed was the most effective with tamoxifen. Ovariectomised athymic mice with established tumours were given tamoxifen with normal diet as control, or the control diet supplemented with secoisolariciresinol diglucoside (SDG), an antioxidant phyto-oestrogen, or flaxseed oil. On trial completion, tumour cells were examined for cell proliferation,