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A pharmacological review of selective oestrogen receptor modulators

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Selective oestrogen receptor modulators (SERMs) are structurally diverse non-steroidal compounds that bind to oestrogen receptors and produce oestrogen agonist effects in some tissues and oestrogen antagonist effects in others. SERMs are being evaluated for a number of oestrogen-related diseases, including post-menopausal osteoporosis, hormone-dependent cancers, and cardiovascular disease. Several compounds that exhibit a SERM profile are currently available for clinical use, including clomiphene, tamoxifen, and toremifene (which are triphenylethylenes) and raloxifene (a benzothiophene). Clomiphene is used for the induction of ovulation in sub-fertile women attempting pregnancy. Tamoxifen and toremifene are both used to treat breast cancer. Tamoxifen may have beneficial effects on bone mineral density and serum lipids. The effects of toremifene on serum lipids are similar to that of tamoxifen. Both compounds have stimulatory effects on the endometrium. Raloxifene, indicated for the treatment and prevention of post-menopausal osteoporosis, has beneficial effects on bone mineral density and serum lipids, but does not increase the risk of endometrial hyperplasia or endometrial cancer. Recently, raloxifene was shown to reduce the incidence of vertebral fractures in otherwise healthy women with osteoporosis; in the same study, a reduced incidence of breast cancer was also observed. Similar to oestrogens, SERMs increase the incidence of venous thromboembolism. Several newer compounds that exhibit a SERM profile are also in clinical development, including other triphenylethylenes (droloxifene, idoxifene) and benzothiophenes (LY353381·HCl), benzopyrans (EM-800), and naphthalenes (CP-336,156).

Key words: clomiphene/raloxifene/SERMs/tamoxifen/toremifene

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Introduction

The past 10 years have seen an explosion in data supporting an understanding of the oestrogen receptor system and of compounds that interact directly with intracellular oestrogen receptors (McDonnell, 1998). For many years, these compounds were classified simply as oestrogen agonists or antagonists. Several key preclinical and clinical studies provided strong impetus to rethink this classification and to introduce the notion of a new class of compounds, referred to as selective oestrogen receptor modulators (SERMs) (Sato *et al.*, 1994a).

Here we review the key pharmacological, preclinical, and clinical data relevant to SERM compounds currently in clinical use. This includes the four agents currently approved for use in the USA: clomiphene citrate (clomiphene), tamoxifen citrate (tamoxifen), toremifene citrate (toremifene), and raloxifene hydrochloride (raloxifene). There are other reviews published in the current issue of this journal, which focus on the uterine and bone effects of some of these compounds (Cano and Hermenegildo, 2000; Díez, 2000).

The notion of SERM

Tamoxifen is the first anti-oestrogen compound to have been used on a long-term basis (Osborne, 1998). While tamoxifen is clearly an anti-oestrogen in breast tissue, it was found to cause endometrial stimulation and increase the likelihood of endometrial cancer (American College of Obstetricians and

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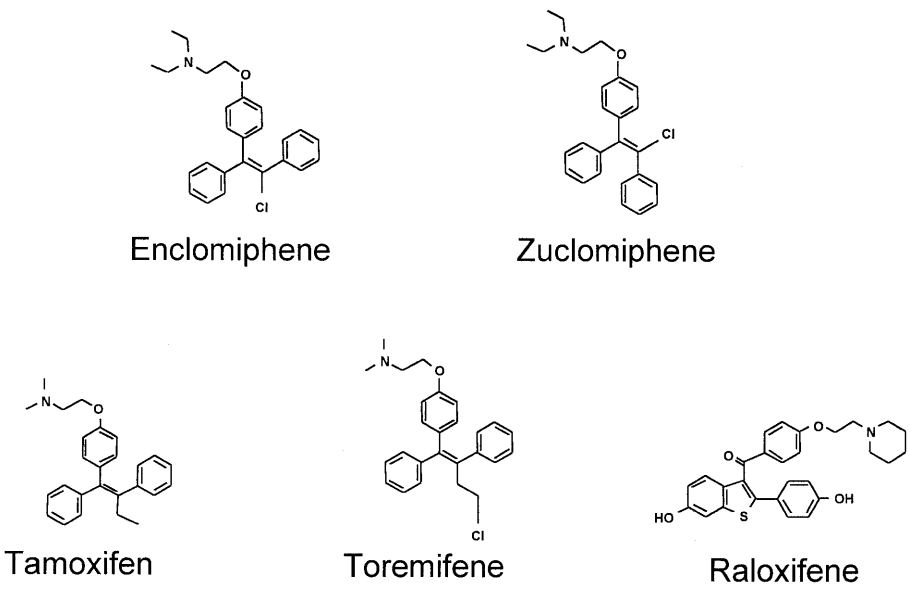

Figure 1. Chemical structures of selective oestrogen receptor modulators currently in clinical use. Both steroisomers of clomiphene (enclomiphene and zuclomiphene) are shown.

Table I. Pharmacological properties of currently available selective oestrogen receptor modulators (SERMs)

	Clomiphene	Raloxifene	Tamoxifen	Toremifene
Half-life in plasma	5 days	28 h	5–7 days	5 days
Primary route of elimination	Faecal	Faecal	Faecal	Faecal
Metabolized by cytochrome *P*-450 pathway	Yes	No	Yes	Yes

Gynecologists Committee on Gynecologic Practice, 1996; Barakat, 1996, 1998). Nonetheless, tamoxifen continued to be considered an 'anti-oestrogen'. Concerns over potential acceleration of osteoporosis, because of its anti-oestrogenic effects, led to studies of bone mineral density in patients who were being treated with tamoxifen for breast cancer (Turken *et al.*, 1989). The data were reassuring, and further studies have supported the notion that tamoxifen is a skeletal anti-resorptive agent in post-menopausal women (Love *et al.*, 1992; Grey *et al.*, 1995b). Concurrent preclinical and clinical work relative to another compound, raloxifene, provided the information necessary to firmly establish the concept of SERMs.

SERMs are a structurally diverse group of compounds that bind to both oestrogen α (ERα) and β (ERβ) receptors and produce oestrogen agonist effects in some tissues, but oestrogen antagonist activity in others (Sato *et al.*, 1994a). The tissue specificity of SERMs is determined in part by the formation of oestrogen receptor–SERM complexes that vary in their ability to activate genes when bound to ERα or ERβ (Paech *et al.*, 1997). Further discussion on the mechanism of action of SERMs is presented elsewhere in this issue.

At present, a number of compounds that possess a SERM profile are in clinical use or in advanced stages of clinical development. By definition, SERMs fulfil the criteria outlined above, while pure anti-oestrogens display only oestrogen antagonistic activity. All of these compounds offer unique profiles that greatly expand therapeutic options in fields ranging from infertility to post-menopausal health.

Structural chemistry and pharmacology of selected SERMs

Compounds currently approved for clinical use that display SERM-like activity fall into one of two chemical families: the triphenylethylenes and the benzothiophenes (Figure 1). Clomiphene, tamoxifen, and toremifene are structurally-related triphenylethylenes. The triphenylethylenes are planar, structurally rigid compounds. They exist in either a *cis*- or a *trans*-conformation and are often used as racemic mixtures. Raloxifene belongs to the benzothiophene family. In contrast to triphenylethylenes, benzothiophenes contain a flexible 'hinge' region, which results in a nearly orthogonal orientation of the basic side chain in raloxifene (Grese *et al.*, 1997). These structural differences appear to account, in part, for differences in the tissue selective actions of benzothiophenes and triphenylethylenes (Grese *et al.*, 1997). The pharmacological properties of these compounds are discussed below and are briefly summarized in Table I.

Clomiphene is a racemic mixture of the two stereoisomers, zuclomiphene and enclomiphene (Adashi, 1993), which vary in proportion, depending on the preparation. For ovulation induction, clomiphene is typically administered daily for 5 days during the follicular phase at a dose of 50 mg/day, but doses of 25–200 mg daily are sometimes used for up to 10 days. Clomiphene is readily absorbed orally in humans and reaches peak plasma concentrations within 6 h (Dickey and Holtkamp, 1996). The half-life of an oral dose of clomiphene is ~5 days, but trace amounts of drug have been found for at least 6 weeks after dosing, suggesting that the drug undergoes enterohepatic recycling (Adashi, 1996; Ginsburg, 1996). The pharmacodynamics of the two isomers are substantially different; enclomiphene is absorbed faster and eliminated more rapidly than zuclomiphene (Adashi, 1996). Clomiphene is metabolized, in part, by the liver and is contra-indicated in patients with liver dysfunction; however, little data exists on the exact pathways involved in clomiphene metabolism (Adashi, 1996). Clomiphene is excreted principally in the faeces and to a lesser extent in urine.

Raloxifene binds to the oestrogen receptor with a K_d of ~50 pmol/l, similar to 17β-oestradiol (Glasebrook *et al.*, 1993). Raloxifene undergoes rapid absorption, extensive first-pass glucuronidation, and enterohepatic cycling after oral administration. There is no evidence that raloxifene is metabolized by cytochrome *P*-450 pathways. Absorption is ~60%, with an absolute bioavailability of 2%. The time to reach average maximum plasma concentration and bioavailability are functions of systemic interconversion and enterohepatic cycling of raloxifene and its glucuronide metabolites. In pharmacokinetic and metabolic studies, raloxifene had a half-life of 27.7 h. Raloxifene is excreted primarily in the faeces (Lilly Research Laboratories, 1999).

Tamoxifen binds to the oestrogen receptor with a K_d of ~2 nmol/l, which is ~20-fold lower than that of 17β-oestradiol (Capony and Rochefort, 1978). Tamoxifen, administered as a single oral dose of 20 mg, is rapidly absorbed and reaches its peak concentration in ~5 h. The terminal elimination half-life is ~5–7 days. Steady-state concentrations in plasma are reached after ~4 weeks of tamoxifen therapy in women. Tamoxifen is extensively metabolized after oral administration; ~65% of the administered dose is excreted over 2 weeks, primarily by faecal excretion. Tamoxifen is excreted mainly as polar conjugates, which account for ~70% of the elimination products. The major metabolite, *N*-desmethyl tamoxifen, is similar in biological activity to tamoxifen (Zeneca Pharmaceuticals, 1998).

Toremifene is a chlorinated derivative of tamoxifen with a similar binding affinity for the oestrogen receptor (Kallio *et al.*, 1986). Toremifene is almost completely absorbed after oral administration, reaches peak concentrations in plasma within 3 h, and has an elimination half-life of ~5 days. Steady-state concentrations of toremifene are reached after ~4–6 weeks of treatment. Toremifene is extensively metabolized, principally by cytochrome *P*-450 3A4 to *N*-demethyltoremifene, and eliminated mainly in the faeces, with ~10% excreted in the urine over a 1 week period (Schering Corporation, 1999).

Preclinical profile

Clomiphene was originally investigated as a contraceptive drug based upon its ability to block ovulation in rodents (Jordan, 1997). Administration of clomiphene to rodents chronically elevates plasma FSH and LH concentrations, which ultimately inhibits ovulation; similar effects are observed in women treated with high doses of clomiphene (Adashi, 1996). Thus, the rodent response to clomiphene indicates that these models are not appropriate for studying the reproductive effects of lower doses of clomiphene in women. Several animal studies indicate that clomiphene has oestrogen agonist effects in the skeleton and cardiovascular system (Beall *et al.*, 1984; Chakraborty *et al.*, 1991; Jimenez *et al.*, 1997). The bone anti-resorptive effect of clomiphene is similar to that of tamoxifen (Beall *et al.*, 1984; Stewart and Stern, 1986). Zuclomiphene and enclomiphene appear to have distinct activities in different tissues. Zuclomiphene is a potent oestrogen agonist in the uterus of ovariectomized rats, while enclomiphene antagonizes the oestrogenic effect of zuclomiphene in this tissue (Young *et al.*, 1991a). Both isomers reduce bone turnover, body weight, and serum cholesterol (Turner *et al.*, 1998).

The distinctive SERM profile of raloxifene has been studied in several animal models in which oestrogen agonist effects in the skeleton and cardiovascular system and oestrogen antagonist effects in the uterus and mammary gland were observed (Bryant *et al.*, 1995; Buelke-Sam *et al.*, 1998). In the ovariectomized rat model of post-menopausal osteoporosis, raloxifene prevented bone loss (Black *et al.*, 1994; Sato *et al.*, 1994b, 1995), reduced cancellous bone resorption (Evans *et al.*, 1996), and increased bone strength (Turner *et al.*, 1994). However, raloxifene did not antagonize the beneficial effects of oestrogen on bone when administered to healthy, ovary-intact rats (Magee *et al.*, 1996). Raloxifene reduced serum cholesterol by ~70% in ovariectomized rats (Black *et al.*, 1994) and inhibited aortic accumulation of cholesterol in cholesterol-fed, ovariectomized rabbits (Bjarnason *et al.*, 1997). In contrast to the rabbit model, raloxifene did not significantly reduce coronary atherosclerosis in ovariectomized cynomolgus monkeys when compared with high doses of conjugated equine oestrogen (Clarkson *et al.*, 1998). However, the study was insufficiently powered and lacked sensitivity to detect a significant effect of raloxifene given that higher than expected blood concentrations of 17β-oestradiol were achieved in the oestrogen-treated group, variability in plaque size was observed, and low sample numbers were used (Bryant *et al.*, 1998). In a separate study, raloxifene inhibited in-vitro oxidation of human low density lipoprotein (LDL) cholesterol more potently than oestrogen (Zuckerman and Bryan, 1996). Raloxifene also induced arterial relaxation in rabbit coronary arteries by an endothelium-dependent mechanism involving nitric oxide (Figtree *et al.*, 1999). In rats and rabbits, raloxifene exhibits little or no effect on uterine weight, uterine histology, and eosinophil peroxidase activity, a sensitive marker of oestrogenic stimulation of the uterus (Black *et al.*, 1994; Sato *et al.*, 1996; Bjarnason *et al.*, 1997). Raloxifene has anti-oestrogenic activity in in-vivo and in-vitro mammary tumour models. Raloxifene inhibited oestrogen-dependent proliferation of MCF-7 human mammary tumour cells *in vitro* (Wakeling *et al.*, 1984) and blocked growth of carcinogen-induced mammary tumours in rats (Clemens *et al.*, 1983).

The anti-oestrogenic action of tamoxifen in mammary tissue has been studied extensively in both cell culture and animal models. Tamoxifen inhibited the oestrogen-stimulated growth of MCF-7 human mammary tumour cells both *in vitro* (Wakeling *et al.*, 1984) and when these cells were implanted into athymic mice (Gottardis *et al.*, 1988). Tamoxifen also inhibited the growth of carcinogen-induced rat mammary carcinomas (Wakeling and Valcaccia, 1983). Tamoxifen treatment protected against bone loss caused by ovariectomy in rats as shown by biochemical bone markers (Frolik *et al.*, 1996) and bone mineral density (Sato *et al.*, 1996). However, tamoxifen markedly reduced the bone conserving action of oestrogen when both were given together (Kalu *et al.*, 1991). Tamoxifen reduced cholesterol concentrations by 50–60% in ovariectomized rats (Frolik *et al.*, 1996; Sato *et al.*, 1996). In ovariectomized monkeys, tamoxifen inhibited the rate of arterial accumulation of LDL degradation products overall and decreased hepatic cholesterol content (Williams *et al.*, 1997). Tamoxifen increased plasma concentrations of triglycerides and reduced average LDL molecular weight, but had no effects on plasma total, LDL, or high density lipoprotein (HDL) cholesterol concentrations (Williams *et al.*, 1997). Coronary artery atherosclerosis was also reduced with tamoxifen treatment, although the effect was not statistically significant (Williams *et al.*, 1997). In the uterus of immature or ovariectomized rats, tamoxifen manifests partial oestrogen agonist effects both on uterine weight and histology (Wakeling and Valcaccia, 1983; Wakeling *et al.*, 1983; Sato *et al.*, 1996). Tamoxifen is a strong hepatocarcinogen in rats, a characteristic that is correlated with its ability to co-valently bind DNA, resulting in hepatic DNA adduct formation (Li *et al.*, 1997). High doses of tamoxifen have been shown to induce cataracts in rats (Greaves *et al.*, 1993).

The preclinical profile of toremifene appears to be similar to that of tamoxifen. Toremifene blocked oestrogen-stimulated growth of MCF-7 breast cancer cells grown in tissue culture (Grenman *et al.*, 1991) or implanted in athymic mice (Robinson and Jordan, 1989) with an efficacy similar to that of tamoxifen (Wakeling *et al.*, 1984; Gottardis *et al.*, 1988). The inhibitory effect of toremifene on the growth of carcinogen-induced rat mammary carcinomas is also comparable with that of tamoxifen (Wakeling and Valcaccia, 1983; di Salle *et al.*, 1990). However, the minimal effective dose of toremifene is higher than that of tamoxifen, which is consistent with the larger dose of toremifene (60 mg/day) that is used clinically as compared with tamoxifen (20 mg/day) (di Salle *et al.*, 1990). In rats, toremifene inhibited ovariectomy-induced bone loss and stimulated the uterus, similar to tamoxifen (di Salle *et al.*, 1990; Karlsson *et al.*, 1999). One of the major differences between toremifene and tamoxifen relates to hepatocarcinogenicity in animal models. Whereas tamoxifen is a strong hepatic carcinogen, toremifene is not hepatocarcinogenic (Hard *et al.*, 1993), and does not form DNA adducts in the rat liver (Hard *et al.*, 1993; Li *et al.*, 1997). Thus far, no studies have shown cataract induction by toremifene (Karlsson *et al.*, 1996).

SERMs in clinical use

Clomiphene

When clomiphene was introduced clinically in the early 1960s (Greenblatt *et al.*, 1961), it revolutionized the treatment of infertility. Clomiphene, now one of the most widely used drugs in the management of infertility, is approved in the USA for the treatment of ovulatory dysfunction in women desiring pregnancy (Clomid®; Hoechst Marion Roussel or Serophene®; Serono). Clomiphene plays a limited role in ovulation induction for various assisted reproductive techniques, for which gonadotrophins have been found to induce a more intense ovarian response (Tarlatzis and Grimbizis, 1998). Clomiphene's primary mechanism of action is antioestrogenic effects in the hypothalamus, where it enhances the release of gonadotrophin-releasing hormone (GnRH). As a result, FSH and LH are released by the pituitary, leading to ovulation (Adashi, 1996). In addition, clomiphene displays antioestrogenic activity in the endometrium and on endocervical cells (Adashi, 1996).

The primary clinical use of clomiphene has been repeated courses of 5–10 days therapy in premenopausal women for the management of infertility. Further additional clinical effects of clomiphene have been explored. There is limited evidence for skeletal antiresorptive effects of clomiphene (Young *et al.*, 1991b). Little clinical evidence is available about the effects of clomiphene on other target organ systems, such as in the cardiovascular system or mammary gland. Similarly, most of the effects of clomiphene on the genital tract and ovaries have been studied only in the context of fertility therapy.

Use of clomiphene for infertility treatment has been associated with few adverse events. The most common adverse events reported are hot flushes and visual disturbances (Asch and Greenblatt, 1976; Adashi, 1996). Hot flushes occur in ~10% of patients (Jones and De Moraes-Ruehsen, 1965). Visual disturbances occur in <2% of patients (Asch and Greenblatt, 1976); while generally reversible, a few reports have suggested that the problem may be permanent (Purvin, 1995). Visual disturbances during clomiphene therapy are possibly due to vascular sludging, which leads to ischaemic optic neuropathy (Lawton, 1994). Other side-effects associated with clomiphene include cervical mucus abnormalities and luteal phase deficiency (Derman and Adashi, 1994).

Raloxifene

Raloxifene (Evista®, Eli Lilly and Company) was approved in the USA in late 1997 for the prevention of post-menopausal osteoporosis, and more recently, for the treatment of post-menopausal osteoporosis. Other areas of study include reduction in risk of breast cancer and cardiovascular disease in post-menopausal women. Raloxifene acts as an oestrogen agonist in the skeleton, on serum lipid metabolism, and on a number of coagulation factors, while it is an oestrogen antagonist in the breast and uterus (Delmas *et al.*, 1997).

Like oestrogen, raloxifene acts as a skeletal antiresorptive to decrease bone turnover and prevent bone loss in post-menopausal women both with (Ettinger *et al.*, 1999) and without (Delmas *et al.*, 1997; Bjarnason *et al.*, 1998) osteoporosis. Raloxifene also reduces the risk for vertebral fractures in women with and without existing vertebral fractures (Ettinger *et al.*, 1999).

Raloxifene has oestrogen agonist effects on lipid metabolism. The effect of raloxifene on lipoproteins and clotting factors was evaluated in a 6-month, double-blind, randomized trial of 390 post-menopausal women. Overall, raloxifene favourably altered biochemical markers of cardiovascular risk, as evidenced by

significant decreases in serum total and LDL cholesterol, without effects on HDL cholesterol, but without increasing triglycerides (Walsh *et al.*, 1998). Similar effects were observed in a larger (n = 601) osteoporosis prevention trial, wherein the effects were maintained for up to 3 years (Delmas *et al.*, 1997; Bjarnason *et al.*, 1998). Raloxifene also significantly decreased fibrinogen and lipoprotein (a) concentrations and increased HDL_2 cholesterol concentrations, but did not significantly affect plasminogen activator inhibitor–1 concentrations (Walsh *et al.*, 1998). Plasma concentrations of homocysteine, an established independent risk factor for atherosclerosis and thromboembolic disease, and C-reactive protein, a non-lipid marker of atherosclerosis, were also decreased by raloxifene (Mijatovic *et al.*, 1998; Paul *et al.*, 1998).

While oestrogens have effects on lipid profile similar to those of raloxifene, and many observational studies have indicated a reduction in coronary heart disease with oestrogen therapy, a recently published large, double-blind, placebo-controlled trial (Heart and Oestrogen/Progestin Replacement Study; HERS) failed to demonstrate any benefit of hormone replacement therapy (HRT) on the secondary prevention of coronary heart disease (Hulley *et al.*, 1998). These results highlight the need for properly-designed, large-scale, randomized, controlled trials to determine the clinical cardiovascular effects of medications altering cardiovascular risk factors. The potential cardioprotective effects of raloxifene are being tested in the Raloxifene Use for The Heart (RUTH) trial (10 000 post-menopausal women). This cardiovascular outcomes study will last 5–7.5 years and has as one of its primary endpoints, combined coronary death and nonfatal myocardial infarction (Barrett-Connor *et al.*, 1998). Primary and secondary prevention of other coronary events will also be examined. In addition, the trial will assess the incidence of breast cancer, osteoporotic fractures, venous thromboembolism, and overall safety.

In contrast to its oestrogen agonist effects on bone and lipid metabolism, raloxifene acts as an oestrogen antagonist in the breast. Raloxifene administration is not associated with an increased incidence of breast pain or tenderness (Davies *et al.*, 1999). More importantly, in the Multiple Outcomes of Raloxifene (MORE) trial, which enrolled 7705 women (mean age, 66.5 years) with osteoporosis and no history of breast cancer, a median of 40 months of raloxifene therapy decreased the incidence of all breast cancer by 76% [relative risk (RR) 0.24, 95% confidence interval (CI), 0.13, 0.44] (Cummings *et al.*, 1999). This reduction was largely due to a 90% reduction in the occurrence of oestrogen-receptor positive tumours (RR 0.10, 95% CI 0.04, 0.24); raloxifene had no significant effect on the frequency of oestrogen-receptor negative tumours (RR 0.88, 95% CI 0.25, 3.0). Based on these analyses, 126 women would need to be treated for a median of 40 months to prevent one case of invasive breast cancer (Cummings *et al.*, 1999).

These data concerning the effects of raloxifene on breast cancer risk may be even more compelling because women with low bone density (required for enrolment in raloxifene trials) reportedly have a decreased risk of breast cancer (Cauley *et al.*, 1996). It is important to note that the routine mammographic screening in the raloxifene trials may have increased detection of breast cancer, offsetting any decreased risk associated with low bone mass. Because it may take years for a breast cancer to become clinically or radiographically apparent, tumours diagnosed in the first 33–40 months of these trials possibly existed at the start of the trial. Thus, the reduction in breast cancer risk observed with raloxifene could represent suppression or regression of subclinical cancer (Cummings *et al.*, 1999).

While tamoxifen is the only therapy currently approved for the reduction in risk of breast cancer in women at high risk for the disease (Nolvadex®; Zeneca Pharmaceuticals, or as a generic version; Barr Pharmaceuticals), the extent to which raloxifene decreases the risk of breast cancer in post-menopausal women at increased risk will be studied in a head-to-head comparison with tamoxifen. The Study of Tamoxifen and Raloxifene (STAR), sponsored by the National Cancer Institute, will enrol 22 000 healthy, post-menopausal women who are at increased risk for breast cancer. The STAR trial, which is scheduled for completion in 2005, will assess the effect of 5 years of therapy on the occurrence of invasive breast cancer (primary endpoint) and on non-invasive breast cancer and endometrial cancer (secondary endpoints).

Because of the known uterine stimulatory effects of oestrogen and triphenylethylene SERMs, uterine safety was carefully monitored in all raloxifene clinical trials. As much as 3 years of therapy with raloxifene did not increase endometrial thickness or increase the incidence of vaginal bleeding, endometrial hyperplasia or endometrial cancer (Huster *et al.*, 1996; Delmas *et al.*, 1997; Scheele *et al.*, 1997; Davies *et al.*, 1998; Cummings *et al.*, 1999; Goldstein *et al.*, 1999).

In clinical trials with doses of 30–600 mg/day, raloxifene was generally well tolerated. The most common side-effects were hot flushes and leg cramps. In an integrated analysis of five randomized, placebo-controlled, raloxifene trials of healthy, post-menopausal women (most were <60 years), women receiving raloxifene had a significantly higher incidence of hot flushes (25%) compared with those receiving placebo (18%) (Lu *et al.*, 1998; Davies *et al.*, 1999). However, there was no therapy difference for the reported severity of hot flushes or for discontinuations due to hot flushes. After the first 6 months of therapy, the increase of new-onset hot flushes was no longer significant for raloxifene (Lu *et al.*, 1998; Davies *et al.*, 1999). The relative risk of hot flushes during raloxifene administration was not influenced by age, years post-menopause, prior HRT use, or presence of hot flushes at entry (Lu *et al.*, 1998). In the older MORE cohort (mean age, 66.5 years), hot flushes were reported less often overall (by 6.4 and 9.7% of the placebo and raloxifene 60 mg groups respectively) (Cummings *et al.*, 1999), although the therapy difference was still significant. Leg cramps associated with raloxifene administration (5.5% for raloxifene 60 mg compared with 1.9% for placebo, $P < 0.05$) were generally mild in nature and did not result in any discontinuation from the study (Davies *et al.*, 1999). The leg cramps reported in clinical trials appear to be idiopathic, as they were not related to mineral imbalance, vascular insufficiency, or venous thrombosis. A rare, but serious, side-effect associated with raloxifene is venous thromboembolism, including deep vein thrombosis (DVT), pulmonary embolism (PE), and retinal vein thrombosis. In osteoporotic women, the relative risk of DVT and PE was 3.1 times higher for the raloxifene group compared with the placebo group (95% CI 1.5, 6.2) (Cummings *et al.*, 1999). This increased

risk is similar to that observed for tamoxifen (Fisher *et al.*, 1998) and oestrogens in observational studies and controlled trials (Castellsague *et al.*, 1998; Hulley *et al.*, 1998). The large-scale study of raloxifene has focused on post-menopausal women, as animal studies have highlighted the potential for teratogenic effects (Buelke-Sam *et al.*, 1998). There has been a single pharmacological study reporting acute effects in premenopausal women (Baker *et al.*, 1998). Until further data from clinical studies is available, the use of raloxifene should be limited to post-menopausal women.

Tamoxifen

Tamoxifen, which is marketed in the USA as Nolvadex® (Zeneca Pharmaceuticals) or as a generic version (Barr Pharmaceuticals), is approved as adjuvant therapy for the treatment of axillary node-negative breast cancer in women irrespective of menopausal state and node-positive breast cancer in post-menopausal women. It is also effective in the treatment of metastatic breast cancer in women and men. Recently, tamoxifen has been approved for the reduction in risk of breast cancer in women at high risk. The anti-tumour effect of tamoxifen in the breast involves its ability to antagonize the proliferative action of oestrogen through competitive binding to the oestrogen receptor. Conversely, tamoxifen manifests oestrogen agonist activity in the skeleton, uterus, and on a number of intermediate markers of cardiovascular risk.

Tamoxifen is among the most widely used drugs in the field of clinical oncology. Numerous clinical trials in women aged >50 years diagnosed with breast cancer have shown a benefit on overall survival (Ragaz and Coldman, 1998). In women undergoing surgery for node-negative breast cancer, 5 years of tamoxifen therapy was associated with a significant prolongation of disease-free survival as compared with placebo-treated women (83 versus 77%) (Fisher *et al.*, 1989). Tamoxifen reduced the rate of treatment failure at local and distant sites, tumours in the opposite breast, and the incidence of tumour recurrence after lumpectomy and breast irradiation (Fisher *et al.*, 1989). Before 1990, >37 000 women with operable breast cancer were enrolled in 55 randomized clinical trials of adjuvant tamoxifen therapy. The results of these studies were recently summarized in a meta-analysis conducted by the Early Breast Cancer Trialists Collaborative Group (Early Breast Cancer Trialists' Collaborative Group, 1998). Tamoxifen was associated with a significant reduction in recurrence (26%) and death (14%), compared with placebo after a median follow-up of 10 years. Women who had oestrogen-receptor positive tumours and those treated for at least 5 years had substantially greater gains than did women with oestrogen receptor-negative tumours or <5 years of therapy (Early Breast Cancer Trialists' Collaborative Group, 1998).

Tamoxifen has also been shown to be an effective therapy in the treatment of metastatic breast cancer. Approximately 30% of women with metastatic breast cancer who were treated with tamoxifen had disease regression for an average of 12 months, and in 20% the disease remained stable for at least 6 months (Osborne, 1998). Even for women who have a relapse of disease ≥6 months after discontinuation of tamoxifen treatment, endocrine therapy with tamoxifen is still the initial treatment of choice (Muss *et al.*, 1987).

The most recent meta-analysis of tamoxifen trials examined the effect of duration of therapy on recurrence and death (Early Breast Cancer Trialists' Collaborative Group, 1998). In women with oestrogen-receptor positive tumours, 5 years of adjuvant tamoxifen therapy was found to be superior to 1 or 2 years (Early Breast Cancer Trialists' Collaborative Group, 1998). These findings were confirmed in two clinical trials that compared the duration of therapy directly (Swedish Breast Cancer Cooperative Group, 1996; Current Trials Working Party of the Cancer Research Campaign Breast Cancer Trials Group, 1996). Whether tamoxifen therapy afforded further benefits when used for >5 years was studied in two North American trials (Fisher *et al.*, 1996; Tormey *et al.*, 1996) and a Scottish trial (Stewart *et al.*, 1996). These studies demonstrated that tamoxifen therapy for >5 years was not associated with additional benefits in disease control. Thus, these studies all support the use of adjuvant tamoxifen for a 5 year period.

Since the antitumour activity of tamoxifen in breast cancer patients is thought to be mediated primarily by competitive inhibition of oestrogen binding to oestrogen receptors, the anti-tumour benefits of tamoxifen are obtained primarily by women whose tumours are oestrogen receptor-positive. The response rate for women with oestrogen receptor-negative metastatic breast cancer was only 8%, compared with a 50% response rate in women with oestrogen receptor-positive tumours (Osborne *et al.*, 1980). Other trials have reported inconsistent results. While the first Early Breast Cancer Trialists meta-analysis found a small, but statistically significant reduction (16%) in the recurrence of breast cancer in women with oestrogen receptor-negative tumours, the more recent meta-analysis did not (Early Breast Cancer Trialists' Collaborative Group, 1992; Early Breast Cancer Trialists' Collaborative Group, 1998). Thus, the efficacy of tamoxifen in treating oestrogen receptor-negative tumours remains controversial.

A number of clinical trials have indicated that tamoxifen reduced the incidence of contralateral breast cancer in women with invasive disease (Rutqvist *et al.*, 1991; Early Breast Cancer Trialists' Collaborative Group, 1998). These findings provided the rationale for studying whether tamoxifen was effective in preventing breast cancer. In 1992, the National Surgical Adjuvant Breast and Bowel Project (NASBP) implemented a randomized clinical trial (NASBP P-1 trial) to evaluate the efficacy of tamoxifen therapy in the prevention of breast cancer in women who were considered at high risk (Fisher *et al.*, 1998). Approximately 13 000 women received placebo or tamoxifen 20 mg/day for 5 years. The study found that tamoxifen reduced the risk of both invasive (RR 0.51, CI 0.39–0.66) and non-invasive breast cancer (RR 0.50, 95% CI 0.33–0.77). The risk reduction was due predominantly to a decrease in the number of oestrogen receptor-positive tumours; tamoxifen had no effect on the incidence of oestrogen receptor-negative tumours (Fisher *et al.*, 1998). Interestingly, two randomized European trials reported no effect of tamoxifen in the reduction in risk of breast cancer (Powles *et al.*, 1994; Veronesi *et al.*, 1998). However, a recent technology assessment by the American Society of Clinical Oncology supported a role for tamoxifen therapy in reducing the risk of breast cancer (Chlebowski *et al.*, 1999).

Table II. Selected clinical trials (completed or ongoing) involving selective oestrogen receptor modulators (SERMs)

Trial	No. of Participants
Tamoxifen	
Early Breast Cancer Trialists Collaborative Group (meta-analysis) (Early Breast Cancer Trialists' Collaborative Group, 1998)	7427
NSABP B-24 (Wolmark *et al.*, 1998)	1804
NSABP P-1 (Fisher *et al.*, 1998)	13 388
Italian breast cancer prevention trial (Veronesi *et al.*, 1998)	5408
United Kingdom breast cancer prevention trial (Powles *et al.*, 1994)	2471
Study of Tamoxifen and Raloxifene (STAR)	22 000 (target)
Toremifene	
Metastatic breast cancer	
United States trial (Hayes *et al.*, 1995b)	648
Nordic trial (Pyrhonen *et al.*, 1997)	415
Eastern European trial (Gershanovich *et al.*, 1997)	463
Adjuvant therapy	
Finnish trial (Holli, 1998)	1460 (target)
International Breast Cancer Study Group-Trial 12 (Holli, 1998)	1140 (target)
International Breast Cancer Study Group-Trial 14 (Holli, 1998)	840 (target)
Raloxifene	
Osteoporosis prevention trial (Delmas *et al.*, 1997)	601
Multiple Outcomes of Raloxifene (MORE) Trial (Ettinger *et al.*, 1998; Cummings *et al.*, 1999)	7705
Cardiovascular risk factors (Walsh *et al.*, 1997)	390
Raloxifene Use for the Heart (RUTH) (Barrett-Connor *et al.*, 1998)	10 000 (target)
Study of Tamoxifen and Raloxifene (STAR)	22 000 (target)

The tamoxifen clinical trials involving patients diagnosed with breast cancer are among some of the largest and longest ever done (Table II) (Fisher *et al.*, 1989; Early Breast Cancer Trialists' Collaborative Group, 1998; Osborne, 1998). Thus, while tamoxifen has been studied almost exclusively in breast cancer patients, a number of important clinical observations have been made regarding the effects of tamoxifen in tissues other than the breast. For example, in a small study of post-menopausal women with breast cancer, tamoxifen treatment was associated with preservation of bone mineral density of the lumbar spine and a suppressive effect on urinary markers of bone turnover during a 2 year treatment period (Love *et al.*, 1992). These findings have been supported by subsequent clinical trials (Ward *et al.*, 1993; Grey *et al.*, 1995b; Resch *et al.*, 1998). In the NASBP P-1 trial, tamoxifen therapy was associated with non-significant decreases in the incidence of hip, spine, and Colles' fractures (Fisher *et al.*, 1998). Although a few observational and prospective studies have suggested a beneficial effect of tamoxifen in the skeleton, tamoxifen has not been evaluated prospectively in women with osteoporosis. The effects of tamoxifen in bone remain to be established.

Another area of tamoxifen effect that has received much attention relates to cardiovascular disease. A number of intermediate markers of cardiovascular risk are favourably influenced by tamoxifen while others show little change. Tamoxifen has been shown to reduce serum total and LDL cholesterol while having no effects on HDL cholesterol and triglycerides in both healthy, post-menopausal women (Grey *et al.*, 1995a; Guetta *et al.*, 1995) and in post-menopausal women with breast cancer (Love *et al.*, 1994). Tamoxifen also lowers serum concentrations of homocysteine (Cattaneo *et al.*, 1998; Anker *et al.*, 1995). Clinical work relative to tamoxifen effects on other intermediate markers of cardiovascular disease, such as direct effect on blood vessels, are scant. One small clinical trial showed no effect of tamoxifen on the pulsatility index of cerebral arteries (Penotti *et al.*, 1998). Several trials have examined the effects of tamoxifen on clinical cardiovascular events, including myocardial infarction and coronary artery-related deaths, although not as primary prospective study endpoints (Table III) (McDonald and Stewart, 1991; McDonald *et al.*, 1995). In the Scottish Cancer Trials Breast Group study, the relative risk for myocardial infarction among patients treated with tamoxifen (maximum duration of 14 years) compared with placebo was 0.29 (95% CI

Table III.TTamoxifen and cardiovascular heart disease (CHD)

	No. of patients	Study findings
Scottish Trial (McDonald *et al.*, 1995; McDonald and Stewart, 1991)	1312	Tamoxifen was associated with a decreased rate of fatal myocardial infarction.
Scandinavian Trial (Rutqvist and Mattsson, 1993)	2365	Tamoxifen reduced the incidence of hospital admissions due to cardiac disease.
NSABP B-14 (Costantino *et al.*, 1997)	2553	Tamoxifen was associated with a decrease in the average annual death rate from CHD.
NASBP P-1 (Fisher *et al.*, 1998)	13 388	Tamoxifen had no effect on the average annual rate of ischaemic heart disease.
Early Breast Cancer Trialists Collaborative Group (Early Breast Cancer Trialists' Collaborative Group, 1998)	36 689	Tamoxifen had no effect on death from cardiac or vascular events.

0.12–0.66) for current users and 0.52 (95% CI 0.27–1.0) for ever users (McDonald *et al.*, 1995). The Stockholm randomized, placebo-controlled trial of adjuvant tamoxifen showed a statistically significant reduction in the incidence of hospital admissions due to cardiac disease for tamoxifen-treated patients (relative hazard 0.68, CI 0.48–0.97) (Rutqvist and Mattsson, 1993). The US-based NSABP B-14 trial found comparable results, although the reduced rate of cardiovascular events did not achieve statistical significance (Costantino *et al.*, 1997). The NASBP P-1 study is the first clinical trial of tamoxifen in which cardiovascular mortality events were a prospective study endpoint. No effect of tamoxifen was observed on the annual rate of ischaemic heart disease events; however, the number of events were small and the study was not adequately powered for this endpoint (Fisher *et al.*, 1998). In summary, a significant beneficial effect of tamoxifen on cardiovascular outcomes is not supported by currently available clinical evidence (Chlebowski *et al.*, 1999).

One of the major controversies surrounding the use of tamoxifen relates to its effects on the endometrium. Tamoxifen administration has been associated with a number of benign findings, including endometrial thickening, endometrial polyps, and endometrial cystic atrophy (Barakat, 1998). While these findings are clinically relevant, the most serious uterine condition associated with tamoxifen use is endometrial cancer, which is increased by 2–4-fold relative to placebo when evaluated in large, randomized trials (Fisher *et al.*, 1994; Early Breast Cancer Trialists' Collaborative Group, 1998). Uterine-related symptoms observed during randomized trials of tamoxifen include vaginal bleeding and leukorrhoea (Zeneca Pharmaceuticals, 1998). Further discussions on the uterine effects of tamoxifen are presented elsewhere in this issue.

The most common adverse effects of tamoxifen are menopausal symptoms, including hot flushes and atrophic vaginitis. Vaginal discharge and irregular menses are also reported at increased incidence in tamoxifen-treated women. Retinopathy has been reported in women taking high doses of tamoxifen (Kaiser-Kupfer and Lippman, 1978). Less extensive retinal changes may sometimes occur in some women on conventional doses of tamoxifen, but vision-threatening ocular toxicity is very rarely observed (Nayfield and Gorin, 1996; Gorin *et al.*, 1998). Tamoxifen has been associated with a slightly increased incidence of cataracts (RR 1.14; 95% CI 1.01–1.29); women on tamoxifen were 57% more likely to undergo cataract surgery, compared with those who received placebo (Fisher *et al.*, 1998). Tamoxifen increases the risk of thromboembolic events (Saphner *et al.*, 1991). In the NASBP P-1 trial, the incidence of deep vein thrombosis was increased for women on tamoxifen (RR 1.6; 95% CI 0.91–2.86) (Fisher *et al.*, 1998). Pulmonary embolism also appeared to occur more in the tamoxifen-treated group as compared to the placebo-treated group (RR 3.01; 95% CI 1.15–9.27) (Fisher *et al.*, 1998). This risk is comparable in magnitude with that seen for HRT/ERT (Daly *et al.*, 1996). However, the Stockholm Breast Cancer Study found no difference between the tamoxifen and control groups in terms of hospital admissions due to thromboembolic disease (Rutqvist and Mattsson, 1993).

Toremifene

Toremifene (Fareston®; Schering) is indicated for the treatment of breast cancer in post-menopausal women with oestrogen receptor-positive tumours or tumours of unknown receptor status (Schering Corporation, 1999). Like tamoxifen, the anti-tumour effect of toremifene in the breast is primarily mediated through competitive binding to the oestrogen receptor (Robinson and Jordan, 1989).

Toremifene has been compared with tamoxifen in three prospective clinical trials of previously untreated post-menopausal women with advanced breast cancer: the North American, Eastern European, and Nordic phase III trials (Hayes *et al.*, 1995a; Gershanovich *et al.*, 1997; Pyrhonen *et al.*, 1997). In the North American and Eastern European trials, toremifene (60 mg/day) was as effective as tamoxifen (20 or 40 mg/day) in the treatment of advanced breast cancer (Hayes *et al.*, 1995a; Gershanovich *et al.*, 1997). Both treatments were statistically equivalent with respect to risk for disease progression, survival, and response rate. The Nordic trial showed some difference in response rate between the two treatments (toremifene 31.3%, tamoxifen 37.3%), although the difference was not statistically significant and occurred mainly in patients with ER-unknown tumours (Pyrhonen *et al.*, 1997). Phase III trials have not shown an advantage of higher doses of toremifene (200 or 240 mg/day) over standard doses of tamoxifen in these women (Gershanovich *et al.*, 1997).

Several studies have evaluated the efficacy of toremifene as a second-line therapy after tamoxifen for the treatment of advanced breast cancer. In a phase II trial of toremifene (200 mg/day) in women who had either: (i) failed to respond to tamoxifen; (ii) relapsed after a prior tamoxifen response or (iii) relapsed during adjuvant tamoxifen therapy, the objective response rate of toremifene was only 5% (Vogel *et al.*, 1993). In a double-blind cross-over trial of toremifene (240 mg/day) and tamoxifen (40 mg/day), 44 patients were crossed-over to the opposite treatment after disease progression (Stenbygaard *et al.*, 1993). No responses were observed after cross-over. These and other studies (Maenpaa and Ala-Fossi, 1997) suggest that toremifene and tamoxifen are clinically cross-resistant in patients with advanced breast cancer.

Since toremifene has been shown to be as effective as tamoxifen in the treatment of metastatic breast cancer, several clinical trials are currently evaluating its efficacy as an adjuvant therapy for breast cancer. The Finnish Breast Cancer Group is comparing toremifene (40 mg/day) with tamoxifen (20 mg/day) in post-menopausal women with lymph node-positive breast cancer disease (Holli, 1998). An interim analysis (mean follow-up of 18 months) indicated no differences between toremifene and tamoxifen in terms of relapse rates (Holli, 1998). The International Breast Cancer Study Group is also conducting two adjuvant therapy studies of toremifene (60 mg/day) and tamoxifen (20 mg/day) (Holli, 1998). The results of these studies have not yet been published.

Several studies have explored additional properties of toremifene, besides its effect in breast tissue. Toremifene administration appears to have little impact on markers of bone resorption in post-menopausal breast cancer patients and was even associated with a slight trend toward a fall in bone mineral density (Marttunen *et al.*, 1998). Thus, the preliminary data on skeletal metabolism suggest that toremifene does not have important skeletal antiresorptive effects.

The effects of toremifene and tamoxifen on intermediate markers of cardiovascular risk were examined in small clinical trials. At a daily dosage of 60 mg, toremifene reduced serum total cholesterol, LDL cholesterol, and apolipoprotein B to an extent comparable to tamoxifen. By contrast to the neutral effect of tamoxifen on HDL cholesterol, toremifene increased HDL cholesterol concentrations by >10% (Saarto *et al.*, 1996). Another study found comparable effects for toremifene on serum total and LDL cholesterol, but failed to show an increase in HDL cholesterol (Gylling *et al.*, 1995). In summary, early studies suggest that toremifene has effects on the lipid profile similar to those of tamoxifen.

Little clinical evidence is available about the effects of toremifene on the uterus and endometrium, especially in terms of the risk for endometrial carcinoma or hyperplasia. The limited published information suggests that toremifene and tamoxifen have comparable stimulatory effects, but this will need to be studied through appropriate clinical trials (Tomas *et al.*, 1995).

The most common adverse events associated with toremifene include hot flushes, vaginal discharge, and nausea (Gershanovich *et al.*, 1997; Maenpaa and Ala-Fossi, 1997). Dizziness, oedema, vaginal bleeding, and vomiting have also been noted in small percentages of women. In the trials that directly compared toremifene and tamoxifen, there were no significant differences between the two therapies in these adverse events. A rare event associated with both toremifene and tamoxifen is the development of reversible corneal opacification, which occurs with comparable frequencies when standard doses are compared (Gershanovich *et al.*, 1997; Pyrhonen *et al.*, 1997). However, high-dose toremifene (200 mg/day) was associated with a higher incidence of corneal opacification than was tamoxifen (Hayes *et al.*, 1995b). The incidence of venous thromboembolism is most likely comparable with that described for tamoxifen, but the size of clinical trials to date is too limited to draw a definite conclusion on this issue (Gershanovich *et al.*, 1997; Pyrhonen *et al.*, 1997; Buzdar and Hortobagyi, 1998). Ongoing and future studies should establish the full clinical profile of toremifene.

Development of new SERMs

Other SERMs recently in clinical development include idoxifene (SmithKline Beecham), droloxifene (Pfizer), CP 336,156 (Pfizer), EM-800 (Schering Plough), GW 5638 (Glaxo Wellcome), MDW 103323 (Hoechst), TSE-424 (Wyeth Ayerst/AFP), and LY353381·HCl (Eli Lilly and Company). Several of these represent new chemical entities, such as benzopyrans and naphthalenes, that appear to display SERM-like profiles. These new compounds are being evaluated for a number of oestrogen-related diseases, including post-menopausal osteoporosis, hormone-dependent cancers, and cardiovascular disease. At present, there is limited information on the clinical efficacy and safety of these compounds.

Conclusions

Oestrogen receptor ligands have been in clinical use for ~40 years. Some of these compounds were originally classified as 'anti-oestrogens' based upon their activities in specific tissues. Raloxifene was the first compound to be classified as a selective oestrogen receptor modulator; other molecules, both older and those more recently developed, have also demonstrated oestrogen receptor-mediated, tissue-specific activity. By definition, SERMs have oestrogen agonist activity in some tissues and oestrogen antagonist activity in others, but the exact profile of effects varies among SERMs. Thus, the potential clinical uses of these compounds will depend largely on their specific tissue profiles.

Clomiphene continues to be a leading compound in the management of infertility. At its clinically relevant site of action, the hypothalamic–pituitary–gonadal axis, clomiphene is primarily an oestrogen antagonist. Raloxifene is the first SERM to be approved for the treatment and prevention of post-menopausal osteoporosis. It is an effective agent for the prevention of vertebral fractures in post-menopausal women with established osteoporosis. The favourable effect of raloxifene on cardiovascular risk factors suggests that it may have cardioprotective effects. The efficacy of raloxifene to prevent coronary artery disease will be determined in the currently enrolling RUTH trial. Raloxifene reduced the incidence of breast cancer in post-menopausal women with osteoporosis. The recently initiated STAR trial will compare the beneficial effect of raloxifene with tamoxifen in the reduction of risk of breast cancer in women who are at high risk for developing the disease. Finally,

raloxifene does not increase the risk of endometrial hyperplasia or endometrial cancer in post-menopausal women. The overall profile of raloxifene makes it a prime therapeutic agent for post-menopausal women at risk of or suffering from osteoporosis. Tamoxifen is one of the most effective agents for the treatment of hormone-responsive breast cancer, and is currently the only drug approved in the USA for the prevention of breast cancer in women at high risk. A head-to-head comparison of raloxifene and tamoxifen in the STAR trial will establish the relative efficacy and safety of the compounds for this indication. The recent approval of toremifene for the treatment of breast cancer further confirms the usefulness of SERMs in the clinical setting. Large, randomized, placebo-controlled, clinical trials have firmly established the position of SERMs as therapeutic options in the management of a variety of hormone-responsive diseases. The efficacy and safety of these agents are presently being studied in clinical trials that should clarify the longer-term risk/benefit balance of SERM therapies.

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