

Ospemifene for the treatment of dyspareunia associated with vulvar and vaginal atrophy: potential benefits in bone and breast

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Abstract: Ospemifene is a selective estrogen receptor modulator (SERM), or estrogen receptor agonist/antagonist, that was recently approved by the US Food and Drug Administration for the treatment of dyspareunia associated with vulvar and vaginal atrophy, a chronic condition that affects up to 60% of postmenopausal women. Ospemifene is the first and only nonestrogen compound approved for this indication. Compared with other approved SERMs, such as tamoxifen, toremifene, bazedoxifene, and raloxifene, the estrogen-like effects of ospemifene in the vaginal epithelium are unique. This review first discusses the rationale for developing ospemifene, including its mechanism of action, and then focuses on the clinical development of ospemifene for the treatment of dyspareunia associated with vulvar and vaginal atrophy. Included are discussions of the effects of ospemifene on the endometrium, serum lipids, coagulation markers, bone, and breast cancer. In conclusion, ospemifene is a SERM with a unique estrogen agonist/antagonist tissue profile that was recently approved in the US for the treatment of dyspareunia associated with vulvar and vaginal atrophy in postmenopausal women. Ospemifene warrants further clinical investigation for the treatment and prevention of osteoporosis and breast cancer.

Keywords: ospemifene, dyspareunia, vulvar and vaginal atrophy, osteoporosis, breast cancer

Introduction

Ospemifene, Z-2-[4-(4-chloro-1,2-diphenyl-but-1-enyl)phenoxy]ethanol, is a novel nonsteroidal, nonhormonal selective estrogen receptor modulator (SERM). It is hypothesized that the primary mechanism of action of ospemifene is mediated through estrogen receptors.¹ The rationale for developing ospemifene as a therapeutic came from the observation that ospemifene was considered a weak/inactive hormonal metabolite of toremifene. This characteristic led to the hypothesis that developing a less potent hormonal agent could lead to a therapeutic benefit while carrying fewer adverse effects. By defining the dose-response relationship of ospemifene preclinically, a full clinical development program was initiated for osteoporosis and postmenopausal vulvar and vaginal atrophy (VVA). This ultimately led to the approval of ospemifene (60 mg/day orally) as the first nonhormonal, nonestrogen for the treatment of moderate to severe dyspareunia in women with menopausal VVA.

As shown in Figure 1, ospemifene and tamoxifen, both triphenylethylenes, are structurally related. They differ in the side chain, with ospemifene containing a hydroxyl group in place of the tertiary amine of tamoxifen. Similar to toremifene, ospemifene also contains a chlorine atom. Ospemifene can be administered orally, transdermally, or parenterally. Food intake increases the absorption of ospemifene by 2–3-fold, and the calorie or fat content of the meal does not significantly affect the increase in

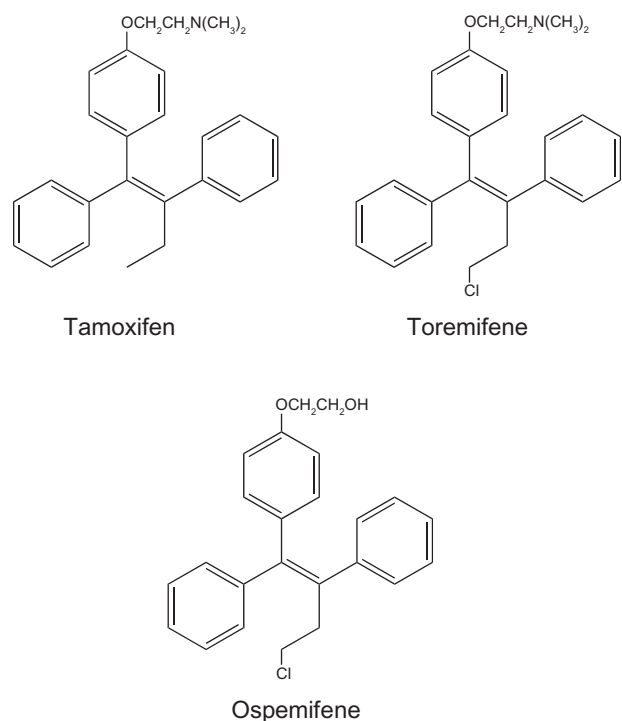


Figure 1 Chemical structures of approved triphenylethylene SERMs, (selective estrogen receptor modulator) ie, tamoxifen, toremifene, and ospemifene.

bioavailability. It is proposed that increased bile production following ingestion of the meal may enhance the solubilization of ospemifene.² Ospemifene is mainly metabolized in the liver, is primarily excreted in the bile, and is eliminated in the feces.^{3,4}

Ospemifene in VVA

Approximately 60% of postmenopausal women who have never been treated with hormone therapy suffer from VVA.⁵⁻⁷ Among women who were treated with hormone therapy in the Women's Health Initiative study, 30% reported the reappearance of symptoms within a week after treatment was discontinued.⁸ Historically, the most effective treatment for VVA has been hormonal therapy with conjugated equine estrogens (Figure 2), which carries a potential risk of stroke, coronary heart disease, thromboembolism, and breast cancer.⁹ Local or vaginal estrogen therapy (17 β -estradiol) is also used for treating women with VVA; however, systemic absorption and associated systemic side effects may still occur.¹⁰⁻¹²

Ospemifene was studied in two Phase II and three Phase III randomized trials as a treatment for VVA.

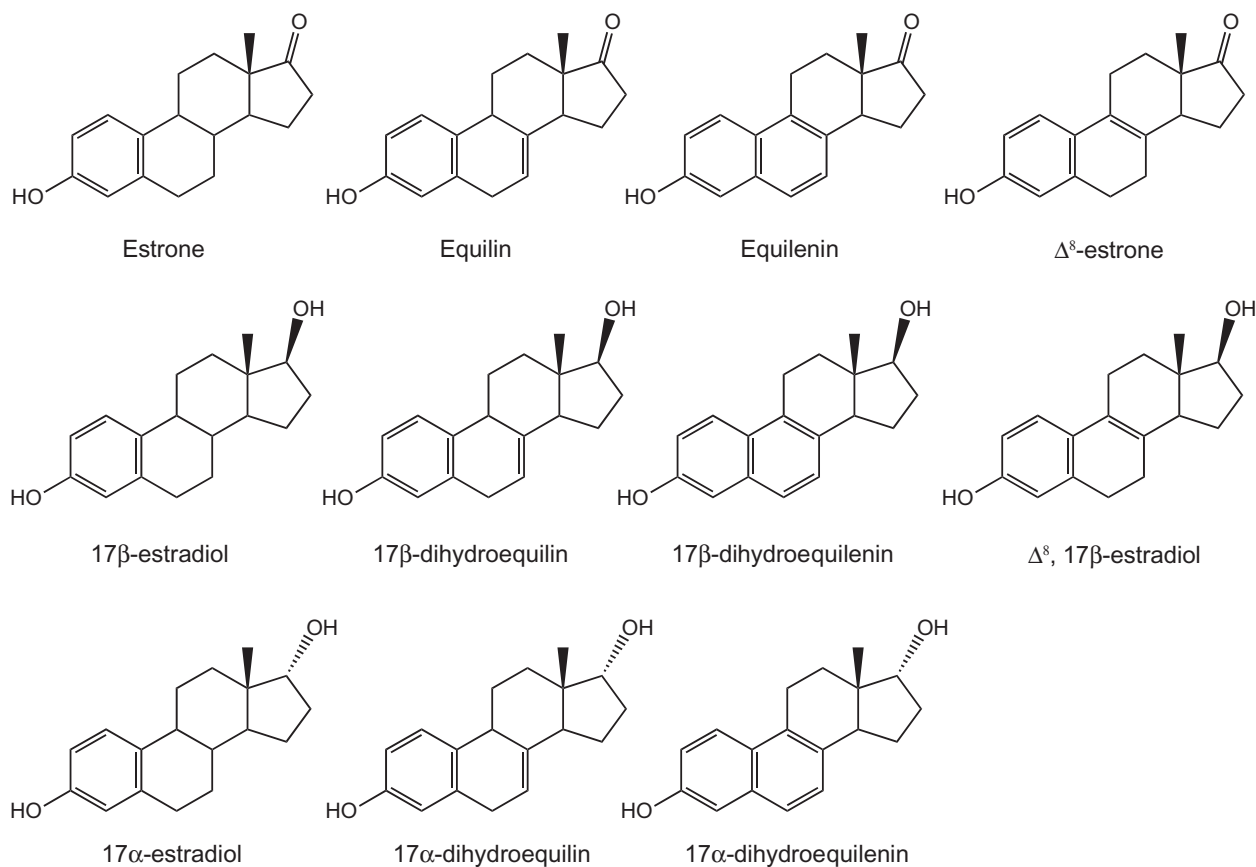


Figure 2 Chemical structures of known steroidal estrogens found in the clinical formulation of conjugated equine estrogens.

In a placebo-controlled, randomized Phase II trial, 160 women were studied after 12 weeks of treatment with ospemifene 30 mg, 60 mg, or 90 mg, or placebo. Women in the ospemifene treatment groups showed significant improvement in superficial and intermediate vaginal epithelial cells in Papanicolaou smears.¹³ Another randomized Phase II trial in 118 participants was conducted to examine the effect of ospemifene on the genital tract in comparison with raloxifene. Ospemifene again showed a clear estrogenic effect on the vaginal epithelium, as reflected by changes in the percentage of cells in the parabasal, intermediate, and superficial layers of Papanicolaou smears. This finding was in sharp contrast with the raloxifene group, which showed no changes from baseline.¹⁴

A pivotal, placebo-controlled, randomized Phase III trial was performed in 826 postmenopausal women at 76 centers across the US. Participants were randomized into three groups to receive either 30 mg/day or 60 mg/day of ospemifene or placebo for 12 weeks.¹⁵ The study showed a highly significant increase in vaginal epithelial cells and a significant decrease in parabasal cells in both ospemifene groups compared with placebo. In addition, significant improvements in the vaginal maturation index were observed within 4 weeks of treatment. Vaginal pH decreased significantly with both doses, but the pH decrease was higher in the group receiving 60 mg/day. After 12 weeks of therapy, the pH decreases were 0.67, 1.01, and 0.10, respectively, in the 30 mg/day, 60 mg/day, and placebo groups.¹⁵

The second placebo-controlled, randomized Phase III trial was performed at 110 sites in the US and included a total of 605 postmenopausal women. This study compared ospemifene 60 mg/day with placebo for 12 weeks.¹⁶ Again, there was a highly significant increase in the percentage of epithelial cells, and highly significant decreases in percentages of parabasal cells and vaginal pH. The most common side effects seen with ospemifene are shown in Table 1. The results of the Phase III trials led to the approval of ospemifene for the treatment of dyspareunia associated with VVA.

Effects of ospemifene on the endometrium

Endometrial safety has been closely examined in all clinical trials performed to date. In a double-blind, placebo-controlled, repeated-dose Phase I study, 40 healthy postmenopausal women were randomized to 25 mg, 50 mg, 100 mg, or 200 mg of ospemifene or placebo for 12 weeks. After 12 weeks, there were no significant changes in endometrial

Table 1 Incidence of more common ($\geq 1\%$) and rare side effects seen with ospemifene (60 mg) treatment compared with placebo

Side effect	Incidence (%)	
	Ospemifene 60 mg (n = 1,242)	Placebo (n = 958)
Hot flashes	7.5	2.6
Vaginal discharge	3.8	0.3
Genital discharge	1.3	0.1
Muscle spasms	3.2	0.9
Hyperhidrosis	1.6	0.6
Stroke		
Hemorrhagic	0.145	0
Thromboembolic	0.072	0.104
Deep vein thrombosis	0.145	0.104

Note: Data from Ospemifene™ (ospemifene) prescribing information.⁴⁴

thickness from baseline, and there were no findings of secretory changes or hyperplasia.¹⁷ All other trials additionally addressed endometrial changes and found very weak estrogenic effects on the endometrium. In the vast majority of participants, the endometrium remained atrophic at the end of 12 weeks of treatment. Overall, a slight increase in rate of proliferation was seen but no hyperplasia was found.¹³⁻¹⁶

The endometrial safety of ospemifene was further assessed in 180 nonhysterectomized postmenopausal women from the initial Phase III trial. These participants were randomized to continue treatment of ospemifene 30 mg/day or 60 mg/day for a total of 52 weeks. At the end of 52 weeks of therapy, endometrial biopsies were performed. There were no cases of endometrial hyperplasia or carcinoma, and the only proliferative findings observed were in one participant each in the 30 mg/day and 60 mg/day treatment groups.¹⁸ These findings confirm the preclinical animal data^{1,19} showing that ospemifene does not have any clinically relevant effects on the endometrium following one year of therapy.

Effects of ospemifene on lipids and coagulation markers

The effect of ospemifene on lipids was examined in two Phase II studies. In the first study, a randomized placebo-controlled trial in 160 healthy postmenopausal women, ospemifene was administered at 30 mg/day, 60 mg/day, or 90 mg/day. There were statistically nonsignificant decreases in total serum cholesterol, low-density lipoprotein, and oxidized low-density lipoprotein, and a nonsignificant increase in high-density lipoprotein. A significant increase in triglyceride levels was seen in the 90 mg/day ospemifene group. There were no significant changes in endothelial

markers or homocysteine levels. However, fibrinogen as a marker for coagulation and fibrinolysis was significantly decreased in the 60 mg/day and 90 mg/day ospemifene groups. No changes were seen in generation of thrombin or D-dimer levels.²⁰

In the other Phase II trial comparing ospemifene with raloxifene, the total cholesterol level was significantly lower in the raloxifene group compared with all ospemifene groups (30 mg/day, 60 mg/day, or 90 mg/day) among a total of 118 participants. The low-density lipoprotein level decreased in the 90 mg/day ospemifene group but not at the 30 mg/day or 60 mg/day dose levels. Raloxifene lowered low-density lipoprotein levels significantly compared with ospemifene 30 mg and 60 mg, but no significant difference was seen between raloxifene and 90 mg/day of ospemifene. No changes in high-density lipoprotein levels were observed in any of the groups. A minor increase in triglycerides was seen in the 90 mg/day ospemifene group.¹⁴ The results of these studies are inconclusive, and need to be added as endpoints in Phase IV studies.

Ospemifene and bone

Results from preclinical studies suggested that ospemifene has potential for the treatment and prevention of osteoporosis.^{1,21} In vitro studies have shown that the effects of ospemifene on osteoclasts are estrogen-like but appear to be distinct from raloxifene.²¹ In vivo, ospemifene was shown to prevent ovariectomy-induced bone loss and maintain bone strength in ovariectomized rats at doses of 1 mg/kg and 10 mg/kg daily for 4 weeks.¹

The effects of ospemifene on serum biochemical markers of bone turnover were evaluated in two Phase II clinical trials in postmenopausal women. In the first trial, ospemifene 30 mg/day, 60 mg/day, and 90 mg/day was compared with raloxifene 60 mg/day, which is the dose approved for osteoporosis, for 12 weeks of treatment. Levels of serum biomarkers for bone resorption, including urinary N- and C-terminal cross-linking telopeptides of type I collagen, serum osteocalcin, bone-specific alkaline phosphatase, and procollagen type I N and C peptides (PINP and PICP, respectively) were not significantly different between raloxifene or ospemifene therapy.^{22,23} A second Phase II study comparing the effect of ospemifene 30 mg/day, 60 mg/day, and 90 mg/day with a placebo group on bone markers supported the findings of the first study. Levels of PINP, PICP, and bone alkaline phosphatase were significantly decreased after treatment with ospemifene compared with placebo.²² These findings strongly suggest that ospemifene has positive

effects on bone markers, justifying further studies aiming to determine if ospemifene lowers fracture rates in women at risk of developing osteoporosis.

Ospemifene and breast cancer

Similar to the development of tamoxifen and toremifene, ospemifene has been extensively studied as an antiestrogen in many preclinical breast cancer models.²⁴ The antiestrogenic activity of ospemifene in breast cancer was recently summarized.²⁵ Given the importance of breast safety during the treatment of VVA with ospemifene, a detailed discussion of these studies is presented.

In a xenograft model where MCF-7 (estrogen receptor-positive) and MDA-MB-231 (estrogen receptor-negative) human breast cancer cells were implanted in nude mice, ospemifene inhibited tumor growth in the implanted MCF-7 cells at oral doses of 10 mg/kg, 25 mg/kg, 50 mg/kg, and 100 mg/kg, whereas no effect was seen in MDA-MB-231 xenografts.^{1,26} These findings support the estrogen receptor-dependent activity of ospemifene.²⁶ In a chemically-induced estrogen receptor-positive breast cancer model, female Sprague Dawley rats were treated with dimethylbenzanthrene, which induces breast cancer in rats. After 7–8 weeks of exposure, the rats were treated with ospemifene at 1 mg/kg, 10 mg/kg, or 50 mg/kg doses orally, and compared with vehicle control. The numbers of breast tumors in the 10 mg/kg and 50 mg/kg dose groups were significantly lower (31% and 5% of those in the vehicle control group, respectively). In the 0.1 mg/kg dose group, a significantly lower number of tumors was only observed after an additional 6 weeks of therapy.¹

In another chemically-induced estrogen receptor + breast cancer mouse model, Sencar mice were used to induce breast cancer with dimethylbenzanthrene. In this study, ospemifene was compared with tamoxifen and raloxifene. Each mouse was subcutaneously implanted with two 20 mg medroxyprogesterone acetate time-release pellets to accelerate the formation of breast tumors. After 6 weeks of exposure to this carcinogen, 50 mg/kg doses of tamoxifen, raloxifene, or ospemifene were given to three different groups of mice for 37 weeks. The incidence of breast tumors was significantly reduced in the tamoxifen and ospemifene groups but not in the raloxifene group.²⁷ In a follow-up study, ospemifene was compared with tamoxifen directly. In this study, treatments were continued for 52 weeks. Of 20 mice in each group, one mouse in the ospemifene and none in the tamoxifen group developed tumors.²⁷ The findings in these chemically induced breast tumor models in rats and mice show that the

chemopreventive effects of ospemifene are comparable with those of tamoxifen.²⁷

The mammary intraepithelial neoplasia outgrowth (MIN-O) mouse model, which resembles human ductal carcinoma in situ, was also used to study the effect of ospemifene in preventing breast cancer. The MIN-O model was derived from polyomavirus middle-T (PyV-mT) transgenic mice. These mice produce stable lines of transplantable MIN-O tissues.^{28–30} Ospemifene was studied in comparison with tamoxifen in transplanted mice. Mice were treated with 50 mg/kg doses of tamoxifen or ospemifene for 7 days prior to transplantation. At 3 and 10 weeks post transplantation, the mice were euthanized and examined. At 3 weeks, there were significantly smaller tumors in both the ospemifene and tamoxifen groups. At 10 weeks, there were significantly fewer breast tumors in both groups compared with control mice. Significantly smaller MIN-Os were also observed in both groups.³⁰

Most recently, the effects of ospemifene in both preventive and treatment settings were evaluated in a PyV-mT transgenic (MTag.Tg) C57BL/6 immunologically intact mouse model of spontaneous breast cancer.³¹ This model is related to the MIN-O model described above, and involves the directed expression of the PyV-mT fusion gene in the mammary tissue of C57BL/6 mice, leading to rapid transformation of mammary tissue.³² As in the MIN-O model, the progression of the cancer in this model has been shown to parallel human breast cancer development histologically and biologically.^{32,33} In this model also, ospemifene was shown to be effective both in prevention of tumor development and also as treatment after tumors were allowed to develop.³¹

These extensive preclinical data strongly suggest that ospemifene and its major metabolite 4-hydroxyospemifene are antiestrogenic in animal models of estrogen receptor-positive breast cancer and ductal carcinoma in situ, with similar activity to tamoxifen. Future studies examining ospemifene as a chemopreventive agent in breast cancer are warranted.

Discussion

Approval of the nonhormonal estrogen agonist/antagonist ospemifene for the treatment of moderate to severe dyspareunia associated with VVA is a breakthrough for postmenopausal women, and is a stimulus for future drug development efforts. Ospemifene is the first nonhormonal estrogen receptor agonist/antagonist approved for this indication. Prior to approval of ospemifene by the US Food and Drug Administration, the only available treatment

options for VVA were lubricants and moisturizers, which fail to address the underlying condition, or locally or systemically administered estrogen-based therapies, which have been the mainstay of treatment for VVA in postmenopausal women for many years.³⁴ Moisturizers and lubricants provide only temporary relief and are largely viewed as messy and cumbersome by postmenopausal women. The use of systemically administered estrogen-based therapies, either in the form of estradiol or conjugated equine estrogens, in hysterectomized women and estrogen plus progesterone in postmenopausal women with an intact uterus, can provide relief from VVA symptoms; however, there are a number of serious side effects associated with these treatments, including stroke, heart disease,^{9,35} and breast cancer,³⁶ and it remains unclear whether estrogen-based therapies are truly effective in treating VVA.^{37,38} While locally administered estrogen-based therapies greatly reduce systemic exposure, systemic absorption still occurs.³⁹

Another candidate for postmenopausal VVA currently being considered for approval by the US Food and Drug Administration is bazedoxifene combined with conjugated equine estrogens (BZA/CE). As a single agent, bazedoxifene is approved in Europe for postmenopausal osteoporosis. In a Phase III clinical trial comparing bazedoxifene alone with BZA/CE and placebo, bazedoxifene alone provided no benefit for VVA and hot flashes.⁴⁰ However, similar to estrogen alone, vasomotor symptoms and VVA were alleviated in postmenopausal women only when combining bazedoxifene with conjugated equine estrogens following 12 weeks of treatment.⁴¹ Therefore, the benefits of this combination are solely attributed to conjugated equine estrogens, which is comprised of a multitude of equine estrogens (Figure 2), and question the wisdom of combining bazedoxifene with conjugated equine estrogens in a 12-week study.⁴² If the intent of bazedoxifene is to protect the endometrium from conjugated equine estrogens in a short course of therapy, this combination shows no potential advantage over ospemifene. Given the well known risks of chronic conjugated equine estrogen therapy reported in the Women's Health Initiative trial, the same risks of stroke, cardiovascular events, breast cancer, and venous thromboembolism may still exist for the BZA/CE combination.⁴³ For example, in regard to breast cancer, whether bazedoxifene will protect breast tissue against conjugated equine estrogens is unknown. For these reasons, the use of BZA/CE for the treatment of VVA in healthy postmenopausal women should be approached with caution until long-term safety data are available well beyond 2 years.

Conclusion

Ospemifene is the first and only nonhormonal agent approved for the treatment of moderate to severe dyspareunia associated with menopause. This breakthrough brings a new nonestrogen alternative therapy for postmenopausal women suffering from the psychosocial and physiological effects of dyspareunia associated with VVA. Additionally, preclinical and clinical evidence suggests that ospemifene may have beneficial effects on bone and breast tissues. Future studies addressing these endpoints, as well as defining the safety profile of prolonged use (greater than one year), may provide support for the expanded use of ospemifene in postmenopausal women.

Disclosure

MWD is one of the original inventors of ospemifene and has a potential conflict of interest. The other authors report no conflicts of interest in this work.

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