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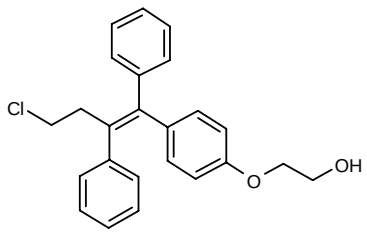
Ospemifene

Prop INN

Treatment of Postmenopausal Syndrome
Treatment of Osteoporosis
Selective Estrogen Receptor Modulator

FC-1271a

2-[4-[4-Chloro-1,2-diphenyl-1(*Z*)-butenyl]phenoxy]ethanol



$C_{24}H_{23}ClO_2$
Mol wt: 378.8967

CAS: 128607-22-7

EN: 289319

Abstract

Osteoporosis and osteoporotic bone fractures are among the most significant disorders afflicting the older female population. Therapeutic options for the treatment and prevention of postmenopausal osteoporosis include hormone replacement therapy (HRT), which has been shown to decrease the risk of nonvertebral fractures but is associated with an increased risk of breast and uterine cancer. Thus, there is a need for selective estrogen receptor modulators (SERMs) that have agonistic, estrogen-like effects on bone and the cardiovascular system but antiestrogenic, antagonistic effects on the uterus and breast. Ospemifene is a novel triphenylethylene SERM that is a major metabolite of toremifene. It is a tissue-specific estrogen or antiestrogen that binds to estrogen receptors α (ERα) and β (ERβ) with affinity comparable to tamoxifen. Ospemifene has been shown to prevent estrogen depletion-induced bone loss in animal models, in addition to inhibiting the growth of human breast cancer MCF7 and DMBA-induced mammary tumors. Ospemifene exerts weak estrogenic and antiestrogenic effects on the uterus, but marked estrogenic effects on bone. In addition, the agent is not associated with the liver toxicity seen with tamoxifen. Ospemifene has demonstrated efficacy and safety in clinical trials in healthy postmenopausal women and is in phase II/III development for the treatment of postmenopausal osteoporosis and urogenital atrophy.

Synthesis

Ospemifene can be synthesized by three related ways:

1) The condensation of desoxybenzoin (I) with 2-(benzyloxy)ethyl bromide (II) by means of aqueous 48% NaOH containing triethylbenzylammonium chloride (TEBAC) gives 4-(benzyloxy)-1,2-diphenyl-1-butanone (III), which by reaction with the Grignard reagent (IV) – prepared from 4-(tetrahydropyranyloxy)phenyl bromide (V) and Mg in THF – yields the triphenylbutanol derivative (VI). Elimination of the THP-protecting group of compound (VI) by means of H_2SO_4 in ethanol/water at room temperature affords the triphenylbutanol derivative (VII), which is debenzylated by hydrogenation with H_2 over Pd/C in ethanol to provide the butane-1,4-diol derivative (VIII). Cyclization of the butane-1,4-diol (VIII) by means of H_2SO_4 in hot ethanol/water gives 2-(4-hydroxyphenyl)-2,3-diphenyltetrahydrofuran (IX), which is treated with 48% HBr in refluxing AcOH to yield a mixture of (*E*)- and (*Z*)-4-(4-hydroxyphenyl)-3,4-diphenyl-3-buten-1-ol (X), which is separated by chemical work up (1). The phenolic OH group of the desired (*Z*)-isomer (X) is condensed with 2-(benzyloxy)ethyl bromide (II) by means of NaOH and tetrabutylammonium bromide in refluxing toluene/water to afford the benzyloxyethyl ether (XII). Reaction of the aliphatic OH group of ether (XII) with PPh_3 and CCl_4 in acetonitrile provides the corresponding chloro derivative (XIII), which is finally debenzylated with H_2 over Pd/C in ethyl acetate/ethanol (2). Scheme 1.

2) Condensation of desoxybenzoin (I) with 2-(tetrahydropyranyloxy)ethyl bromide (XIV) by means of aqueous NaOH and TEBAC as before gives 1,2-diphenyl-4-(tetrahydropyranyloxy)-1-butanone (XV), which by a Grignard condensation with 4-methoxyphenylmagnesium bromide (XVI) –prepared from 4-bromoanisole (XVII) and Mg in THF– provides the triphenylbutanol derivative (XVIII). Cleavage of the THP-protecting group of compound (XVIII) with H_2SO_4 in ethanol/water at room temperature affords the butane-1,4-diol derivative (XIX),

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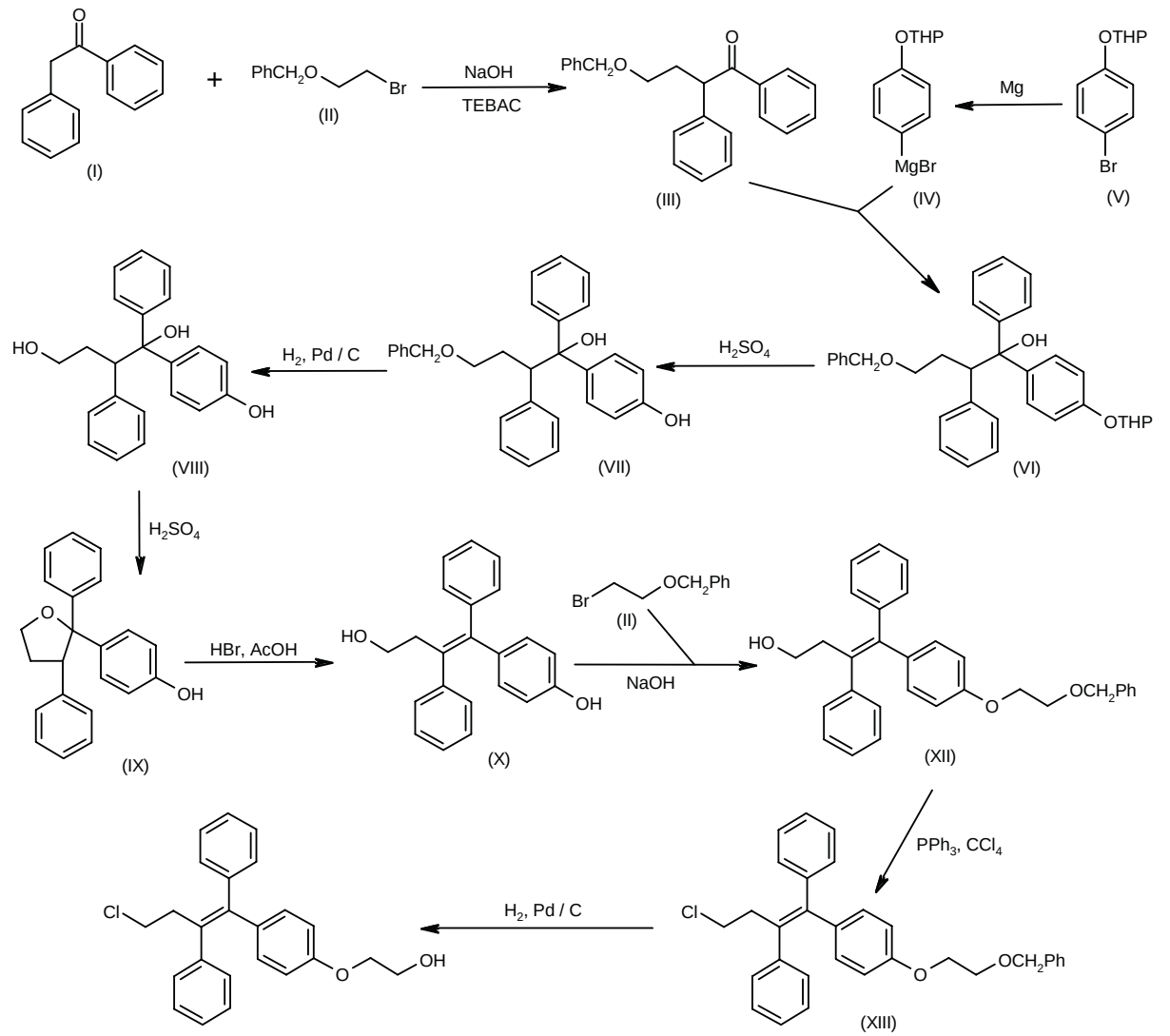
Scheme 1: Synthesis of Ospemifene



which is cyclized by means of H_2SO_4 in hot ethanol/ water to yield 2-(4-methoxyphenyl)-2,3-diphenyltetrahydrofuran (XX). Finally, this compound is treated with 48% HBr in refluxing AcOH to give 4-(4-hydroxyphenyl)-3,4-diphenyl-3-buten-1-ol (X) as a (*Z*):(*E*)-isomeric mixture, from which the desired (*Z*)-isomer is separated by chemical work up (1). Scheme 2.

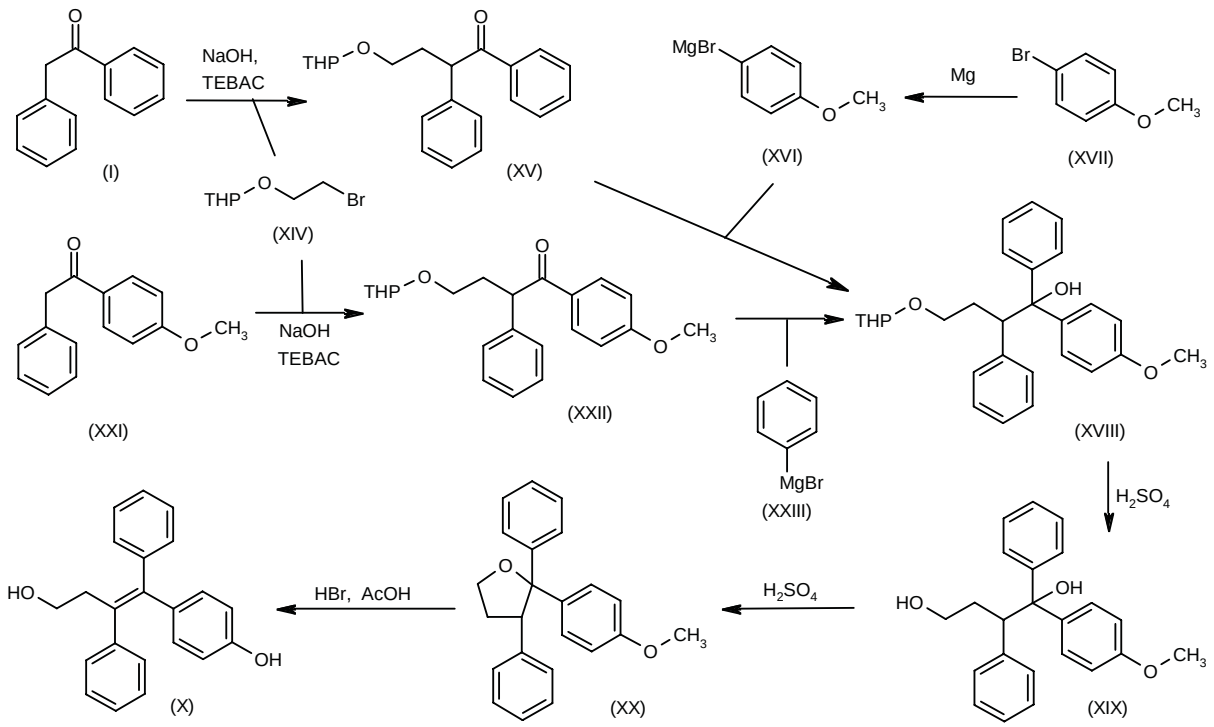
3) Alternatively, the triphenylbutanol intermediate (XVIII) can also be obtained by condensation of 4-methoxydesoxybenzoin (XXI) with 2-(tetrahydropyranyloxy)ethyl bromide (XIV) by means of NaOH and TEBAC as before to give 1-(4-methoxyphenyl)-2-phenyl-4-(tetrahydropyranyloxy)-1-butanone (XXII), followed by treatment with phenylmagnesium bromide (XXIII) in THF (1). Scheme 2.

Introduction

Osteoporosis and osteoporotic bone fractures are among the most significant disorders afflicting the older female population. Approximately 1 in 4 women over the age of 65 develop osteoporosis. The postmenopausal state is accompanied by a reduction in plasma 17β-estradiol to less than 10% of premenopausal values. This estrogen deprivation results in low bone mineral density (BMD), which is responsible for osteoporotic fractures and the significant morbidity experienced in this population (3-7). Research efforts have therefore focused on the therapeutic management of the postmenopausal state in an attempt to improve women's health and quality of life.

Of the therapeutic options currently available, hormone replacement therapy (HRT) has been shown to

Scheme 2: Synthesis of Intermediate (X)



decrease the risk of nonvertebral fractures by 27% (8). Other benefits have been attributed to HRT, including improvements in short-term memory and cognitive function, relief of perimenopausal symptoms (*e.g.*, vasomotor instability, hot flushes, sleep disturbances, genitourinary symptoms) and reductions in the risk of coronary heart disease. Unfortunately, HRT is associated with several adverse events, including bleeding, bloating, breast tenderness and an increased risk for uterine and breast cancer. In addition, the efficacy of HRT in preventing fractures has not been proven and HRT is not approved by the U.S. FDA for the treatment of osteoporosis (3, 9, 10).

Thus, there is a need for selective estrogen receptor modulators (SERMs) that have agonistic estrogen-like effects on bone and the cardiovascular system, along with antiestrogenic, antagonistic effects on the uterus and breast. Tamoxifen was the first clinically available SERM for the treatment and prevention of breast cancer. It has beneficial effects on bone and the cardiovascular system, but is associated with an increased risk of endometrial cancer, hepatocarcinogenesis and deep vein thrombosis (11-13). Toremifene is another triphenylethylene-based SERM that is used in the treatment of metastatic breast cancer. However, it also induces effects in the endometrium similar to tamoxifen (14). Raloxifene is a benzothiophene derivative SERM that has been shown to increase BMD, decrease bone turnover and decrease the risk of vertebral fracture. However, raloxifene either has no effect or may even aggravate hot flushes (15, 16). To date, none of the available SERMs meets all of the requirements of optimal HRT in postmenopausal women. Thus, the search for more effective SERMs continues.

Ospemifene (FC-1271a), a novel triphenylethylene SERM that is a major metabolite of toremifene ([deaminohydroxy]toremifene), is a tissue-specific estrogenic/antiestrogenic agent that binds to estrogen receptors α (ERα) and β (ERβ) with affinity comparable to tamoxifen. Ospemifene has been shown to prevent estrogen depletion-induced bone loss in animal models, as well as inhibiting the growth of human breast cancer MCF7 cells and tumors and dimethylbenzanthracene (DMBA)-induced mammary tumors. It also lowers serum cholesterol levels. Ospemifene exerts weak estrogenic and antiestrogenic effects in the uterus, but marked estrogenic effects on bone. In addition, the agent is not associated with the liver toxicity seen with tamoxifen. Ospemifene was therefore chosen for further development as a treatment for postmenopausal osteoporosis and urogenital atrophy (17).

Pharmacological Actions

In vitro studies comparing the binding of toremifene and its major metabolites, including ospemifene, with tamoxifen reported similar binding affinities for the rat

cystolic ER. Another study examining the ability of ospemifene to compete with 17β-[^{3}H]-estradiol for binding to purified recombinant human ERα and ERβ as compared to unlabeled 17β-estradiol showed that ospemifene displaced estradiol in a concentration-dependent manner (IC_{50} = 827 and 1633 nM *vs.* 6.8 and 9.1 nM for 17β-estradiol for ERα and ERβ, respectively). The calculated relative binding affinities of ospemifene for ERα and ERβ were 0.8% and 06%, respectively (17, 18).

Ospemifene was shown to stimulate bone formation in an *in vitro* study examining the effects on the differentiation of osteoblasts in 21-day mouse bone marrow cultures. Ospemifene, 17β-estradiol and tamoxifen (0.01-10 nM) all stimulated proliferation by day 6 of culture (81%, 48% and 42%, respectively) and increased the specific activity of alkaline phosphatase, a marker of osteoblast differentiation; raloxifene had no effect on proliferation (19). Another study using mouse bone marrow cultures examined the effects of these agents on osteoclast differentiation. Ospemifene was found to have no effect on osteoclast apoptosis at concentrations from 10 pM to 10 μM. However, a concentration-dependent inhibition of osteoclast differentiation was observed (20, 21).

The selective estrogenic effects of ospemifene (0.1-10 mg/kg p.o. for 4 weeks) were demonstrated in a study using intact and ovariectomized 4-month-old rats. Treatment at doses of 1 and 10 mg/kg prevented ovariectomy-induced bone loss via maintenance of trabecular bone volume of the distal femur as compared to vehicle-treated animals. In addition, dose-dependent reductions in serum cholesterol (7-55%) were observed. No changes in uterine weight or morphology were observed with doses of 0.1 or 1 mg/kg, although a slight estrogenic effect was seen at the highest dose. The effects of ospemifene on uterine weight in immature rats were less potent than toremifene or tamoxifen, but it was more stimulatory than raloxifene or droloxifene (17).

The effects of ospemifene, 17β-estradiol, tamoxifen and raloxifene were compared on uterine expression of ER and progesterone receptors (PR) in ovariectomized rats treated with the agents for 10 days. In contrast to 17β-estradiol which increased cell proliferative activity in the luminal and glandular epithelium of the uterus, ospemifene, tamoxifen and raloxifene decreased this activity in both areas. While 17β-estradiol and tamoxifen reduced ERα immunoreactivity in uterine glandular epithelium and slightly decreased it in other uterine compartments, ospemifene had less effect on ERα in the myometrium and glandular epithelium; raloxifene suppressed ERα expression in the stroma and myometrium and abolished expression in glandular epithelium. Ospemifene, 17β-estradiol and tamoxifen all strongly abolished PR immunoreactivity in luminal and glandular uterine epithelium (22).

The effects of ospemifene on breast cancer cells/tumors were examined *in vitro* and *in vivo* in several studies. In one study, ospemifene at concentrations of 0.1 nM to 10 μM did not significantly increase estrogen-dependent human breast cancer MCF7 cell growth or inhibit estradiol-stimulated growth, except for a 30% reduction in estradiol-stimulated growth at the highest concentration of 10 μM. Similar results were obtained with estrogen-dependent human breast cancer ZR-75-1 cells (17). In other *in vitro* studies, treatment of MCF7 cells with ospemifene or its major metabolite (0.1-10 μM) inhibited growth and concentration-dependently reduced the expression of pS2, an estrogen-regulated gene and an indicator of estrogen activity; however, ospemifene had no effect on the growth of ER-negative human breast cancer MDA-MB-231 cells (23, 24). In animal experiments, ospemifene (1, 10 or 50 mg/kg p.o. for 4 weeks) was shown to significantly and dose-dependently inhibit the appearance and growth of DMBA-induced mammary tumors in rats, the number of tumors being 31% and 5% of controls, respectively, at doses of 10 and 50 mg/kg. At follow-up at 6 weeks, rats treated with the higher dose continued to exhibit significantly fewer tumors (35% of controls) (17). Another study compared the chemopreventive effects of ospemifene, tamoxifen and raloxifene in the mouse DMBA-induced mammary tumor model. Both ospemifene and tamoxifen significantly reduced the incidence of mammary tumors, whereas raloxifene did not (24). Treatment of athymic ovariectomized mice bearing human MCF7 tumor xenografts with ospemifene (10, 25, 50 or 100 mg/kg once daily p.o. for 7 days) significantly inhibited tumor growth on days 51 and 58 postimplantation. The agent had no effects on the growth of ER-negative MDA-MB-231 tumors *in vivo* (25).

In contrast to tamoxifen (45 mg/kg p.o. for 2 weeks in rats; 50 mg/kg p.o. or s.c. for 28 days or 50, 100 or 200 mg/kg p.o. for 7 days in mice) which induced the formation of DNA adducts in liver associated with increased hepatocarcinogenicity, no adducts were observed in rats or mice treated with ospemifene (45 mg/kg p.o. for 2 weeks; 50 mg/kg p.o. or s.c. for 28 days or 50, 100 or 200 mg/kg p.o. for 7 days in mice) (17, 26).

Pharmacokinetics and Metabolism

Several HPLC methods have been described and optimized to determine toremifene and its major metabolites, including ospemifene, in human plasma and urine samples (27-31).

The pharmacokinetics of ospemifene were determined in a single-dose (10-800 mg p.o.), dose-escalating phase I study in 28 healthy males and in a 12-week repeated-dose (25-200 mg/day p.o.) phase I study in 40 postmenopausal women. Ospemifene was well tolerated in both studies. Mean values for t_{max}, C_{max} and half-life obtained in the single-dose study were 1.3-4.0 h, 15.0-494.3 ng/ml and 24.8 ± 7 h, respectively; t_{max} and C_{max} values reported in the repeated-dose study at 6 and 12 weeks were 1.9-2.6 and 2.5-2.9 h and 295-1043 and 251-1211 ng/ml, respectively, and the mean $t_{1/2}$ value at all doses was 29.7 ± 1.5 h. A linear correlation was noted between dose and C_{max} and AUC values (32).

Table I: Clinical studies of ospemifene (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Menopause	Randomized, Double-blind	Ospemifene, 25 mg po od x 12 wk (n=8) Ospemifene, 50 mg po od x 12 wk (n=8) Ospemifene, 100 mg po od x 12 wk (n=8) Ospemifene, 200 mg po od x 12 wk (n=8) Placebo (n=8)	40	Ospemifene was safe and well tolerated at doses of 25-100 mg in healthy postmenopausal women	33
Menopause	Randomized, Double-blind, Multicenter	Ospemifene, 30 mg po od x 3 mo (n=40) Ospemifene, 60 mg po od x 3 mo (n=40) Ospemifene, 90 mg po od x 3 mo (n=40) Placebo (n=40)	160	Ospemifene at doses up to 90 mg/d showed no increase in the risk of cardiovascular events in postmenopausal women. Compared with placebo, the only significant differences induced by the drug were an increase in triglyceride levels (for the 90 mg/d dose) and a reduction in fibrinogen levels (for the 60 and 90 mg/d doses). Ospemifene exhibited estrogenic effects on the vaginal epithelium, but did not stimulate the endometrium or aggravate climacteric symptoms such as hot flashes in healthy postmenopausal women	34
Osteoporosis	Randomized, Double-blind, Multicenter	Ospemifene, 30 mg po od x 12 wk Ospemifene, 60 mg po od x 12 wk Ospemifene, 90 mg po od x 12 wk Raloxifene, 60 mg po od x 12 wk	119	Ospemifene might be effective in postmenopausal osteoporosis	35

Clinical Studies

A randomized, double-blind, placebo-controlled phase I study in 40 healthy postmenopausal women examined the effects of ospemifene (25, 50, 100 or 200 mg p.o. for 12 weeks) on uterine endometrium, vaginal maturation index and hormonal status. Ospemifene was safe and generally well tolerated at all dose levels. No significant changes in blood pressure, heart rate, ECG or laboratory parameters were seen with treatment. A higher incidence of subjective adverse reactions such as hot flushes was reported in the group receiving the highest dose as compared to the lower dose levels. Two subjects discontinued prematurely. No clinically significant alterations in endometrial thickness were seen at any dose level. Endometrial histology changed from atrophy to proliferative class I in 1 subject each from the 50-, 100- and 200-mg groups, and 2 subjects with high estradiol levels measured during treatment and receiving 100 and 200 mg showed a change from atrophy to proliferative class II. In contrast, all subjects who presented with atrophic vaginal epithelium at entry exhibited estrogenic effects on vaginal epithelium, including a reduction in the percentage of cells in the parabasal layer (index 1) and an increase in the number of cells in the intermediate (index 2) and superficial (index 3) layers after treatment. Significant differences were seen in vaginal maturation indices 1 and 3. Significant dose-dependent decreases in follicle-stimulating hormone (FSH) and increases in sex hormone-binding globulin (SHBG) were also observed during treatment, but no changes in luteinizing hormone (LH), estradiol, parathyroid hormone (PTH) or prolactin were reported. Climacteric symptoms (hot flushes, sweating, insomnia, depression, headache, vaginal dryness, cardiac symptoms, urinary incontinence, nausea, swelling, breast tenderness and/or fatigue) tended to be reduced in subjects treated with doses of 25 and 50 mg and increased in subjects given doses of 100 and 200 mg, although these changes did not reach significance. Based on these results, doses of 25-100 mg were suggested for clinical use (33). This and the following clinical studies are summarized in Table I.

A randomized, double-bind study conducted in 160 healthy postmenopausal women demonstrated that short-term use of ospemifene (30, 60 or 90 mg p.o. for 3 months) has no effect on the risk of cardiovascular disease in this population. Five subjects discontinued due to adverse events, including 1 subject on 30 mg for headache, 3 subjects on 60 mg for numbness, nausea and amebal infection, and 1 subject on 90 mg for amebal infection. Two subjects were also discontinued for protocol violation or noncompliance. Treatment was concluded to be well tolerated. A decrease from basal levels in total cholesterol levels, low-density lipoprotein (LDL) cholesterol and oxidized LDL, and an increase in high-density lipoprotein (HDL) cholesterol were observed in treated subjects, although these changes did not reach statistical significance. A significant increase in triglyceride levels of 11.3% was observed in the 90-mg group. There were no significant alterations in endothelial markers (*e.g.*, endothelin-1, nitrite, nitrate) or homocysteine in any of the dose groups. In subjects receiving 60 and 90 mg, significant reductions in plasma fibrinogen of 8.7% and 8.5%, respectively, were observed as compared to placebo; no changes in thrombin generation or crosslinked fibrin D-dimer degradation were noted. In addition, uterine and

carotid artery blood flow velocity, 24-h ambulatory blood pressure, basal insulin levels and 2-h glucose tolerance test results were unchanged with treatment (34).

A 12-week, randomized, double-blind study in 120 healthy postmenopausal women compared the effects of ospemifene (30, 60 or 90 mg/day p.o.) with raloxifene (60 mg/day p.o.) Results from analysis of bone metabolism markers suggested similar sparing effects for 60 and 90 mg of ospemifene and raloxifene on bone turnover; the lowest dose of ospemifene had no effect. The two higher doses of ospemifene and raloxifene also reduced serum gonadotropin levels and increased serum SHBG levels during treatment. No significant changes in serum LDL or HDL cholesterol were observed in any treatment group. Neither agent exerted proliferative effects on the endometrium, although an estrogenic effect was observed on vaginal and ectovaginal cells in PAP smear cytological samples from subjects receiving ospemifene. According to Kupperman's indices, all patients given ospemifene, in contrast to only some raloxifene-treated subjects, experienced some relief from menopausal symptoms. Treatment with ospemifene also tended to reduce vaginal dryness compared to raloxifene, as indicated by observations made on a visual analogue scale (35).

Ospemifene is presently undergoing phase II/III development as a treatment for postmenopausal urogenital atrophy and for the prevention and treatment of postmenopausal osteoporosis (36).

Source

Discovered by Orion Corporation (FI); codeveloped with Hormos Medical, Ltd. (FI).

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