Drugs of the Future 2002, 27(10): 942-947

CCC: 0377-8282/2002

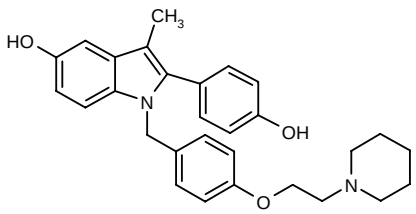
Pipendoxifene

Prop INN

Treatment of Breast Cancer
Estrogen Receptor Modulator

ERA-923

2-(4-Hydroxyphenyl)-3-methyl-1-[4-[2-(1-piperidinyl)ethoxy]benzyl]-1*H*-indol-5-ol



$C_{29}H_{32}N_2O_3$

Mol wt: 456.5828

CAS: 198480-55-6

CAS: 389125-71-7 (as monohydrochloride monohydrate)

CAS: 245124-69-0 (as monohydrochloride)

EN: 272939

Abstract

Breast cancer is the most commonly diagnosed malignancy and the second cause of death in women. In addition to environmental factors, genetic factors appear to play a major role in the development of breast cancer and the risk is high in those individuals with a history of the disease among relatives. Because breast cancer is hormonally dependent and requires low levels of circulating estrogen to thrive, hormonal manipulation to block estrogen-stimulated growth can be an effective treatment against certain forms of breast carcinoma. Available therapies to reduce the detrimental effects of prolonged exposure to estrogen include antiestrogens (also called selective estrogen receptor modulators [SERMs]), nonsteroidal SERMs and selective estrogen enzyme modulators (SEEMs). Although several SERMs with distinct agonist and antagonist pharmacological profiles have been discovered in the last decade, the search continues for compounds with increasingly selective profiles. Pipendoxifene is a new 2-phenyl indole SERM that exhibits an excellent preclinical pharmacological profile and was selected for further development as a treatment for metastatic breast cancer.

Synthesis

Pipendoxifene can be synthesized by two related ways:

a) Alkylation of 4-hydroxybenzaldehyde (I) with 1-(2-chloroethyl)piperidine hydrochloride (II) by means of K_2CO_3 in DMF at reflux affords 4-[2-(1-piperidinyl)-ethoxy]benzaldehyde (III), which is reduced with $NaBH_4$ in MeOH to provide the benzylic alcohol (IV). Alternatively, alcohol (IV) can be obtained by reaction of 4-hydroxybenzyl alcohol (V) with 1-(2-chloroethyl)piperidine hydrochloride (II) by means of NaOH and benzyltriethylammonium bromide in toluene. Alcohol (IV) is first treated with HCl in THF and then chlorinated with $SOCl_2$ to give 1-[2-[4-(chloromethyl)phenoxy]ethyl]piperidine hydrochloride (VI), which is condensed with the indole derivative (VII) – obtained by condensation of the bromo ketone (VIII) with 4-benzyloxyaniline hydrochloride (IX) by means of either refluxing DMF (1) or Et_3N in refluxing DMF (2) – by means of NaH in DMF to give the *N*-alkylated indole (X). Finally, the *O*-benzyl protecting groups of (X) are removed by transfer hydrogenolysis using cyclohexadiene and Pd/C (1). Scheme 1.

b) Reaction of 4-hydroxybenzyl alcohol (V) with ethyl 2-bromoacetate (XI) by means of K_2CO_3 provides the phenoxyacetate (XII), which is then treated with $SOCl_2$ in THF to give the benzyl chloride (XIII) (2). Reaction of compound (XIII) with the indole derivative (VII) by means of NaH in DMF yields the adduct (XIV), which is reduced at the ester group with $LiAlH_4$ in THF to afford 5-(benzyloxy)-2-(4-benzyloxyphenyl)-1-[4-(2-hydroxyethoxy)benzyl]-3-methyl-1*H*-indole (XV). Treatment of indole (XV) with CBr_4 and PPh_3 in THF provides the 2-bromoethoxy derivative (XVI), which by reaction with piperidine (XVII) in THF is converted into the 2-(1-piperidinyl)ethoxy derivative (XVIII). Finally, compound (XVIII) is debenzylated by hydrogenation with either H_2 over Pd/C in ethanol/THF (2, 3) or with cyclohexadiene and Pd/C in THF/EtOH (3). Scheme 2.

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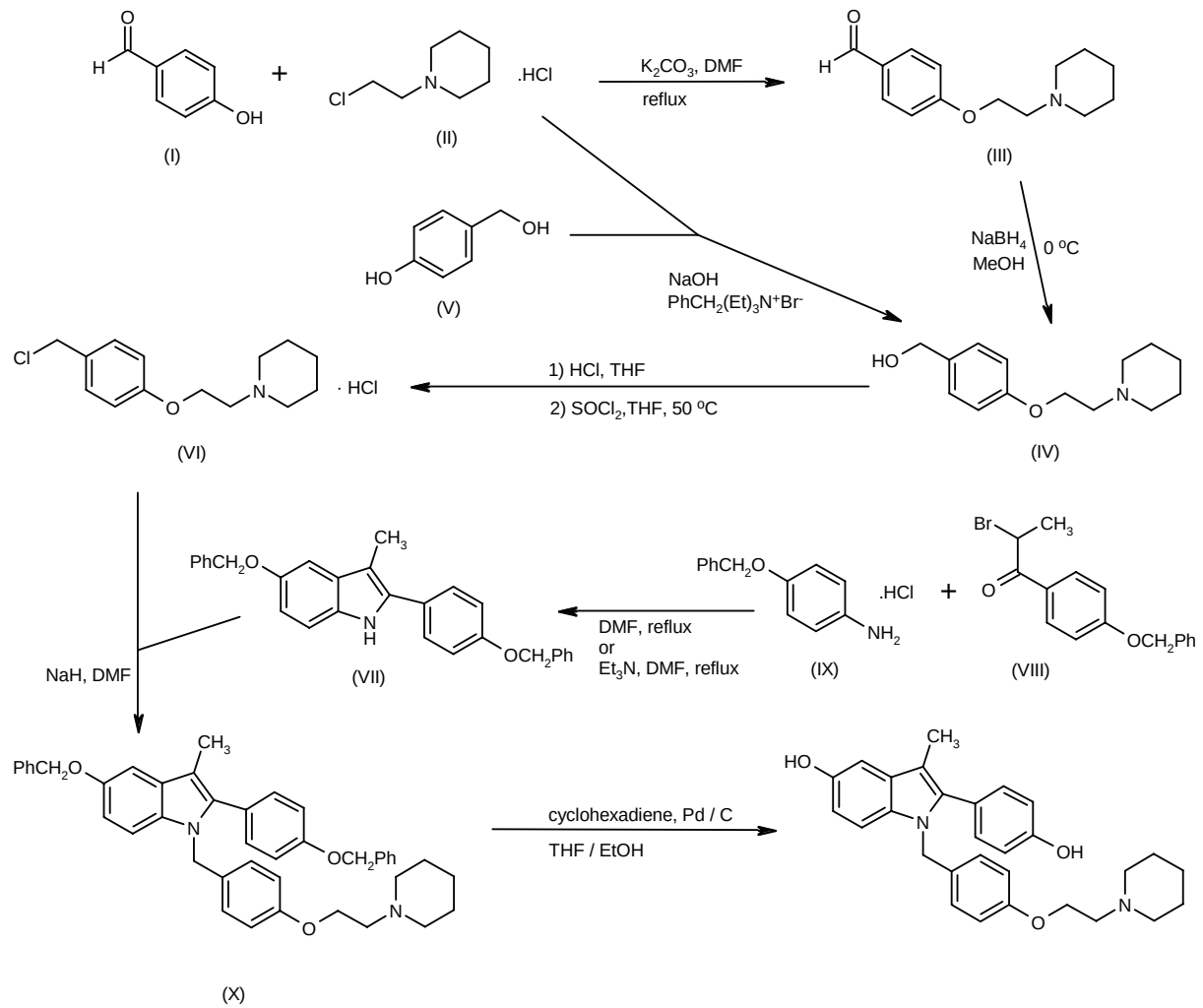
Scheme 1: Synthesis of Pipendoxifene

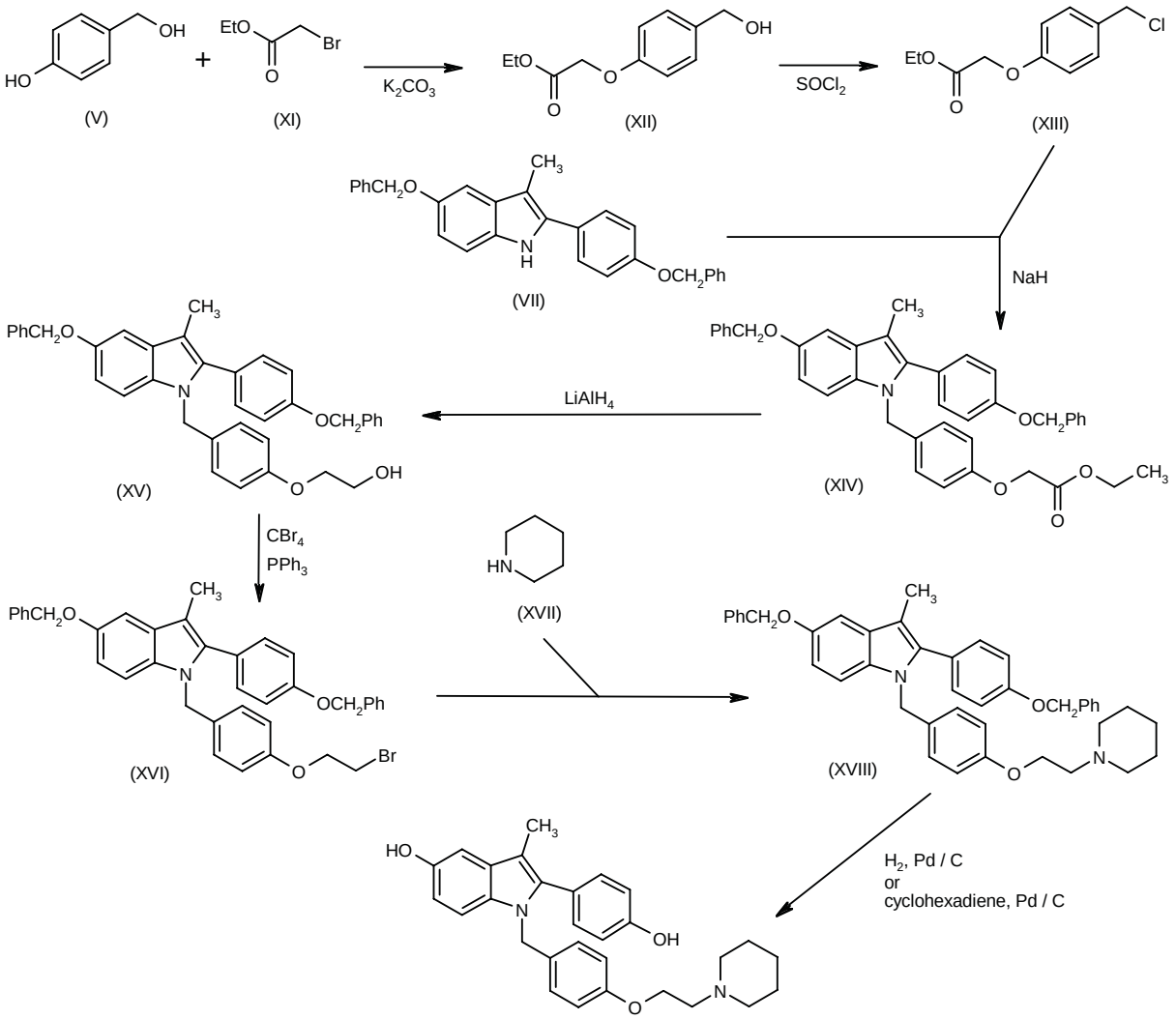


Introduction

Breast cancer is the most commonly diagnosed malignancy and second cause of death in women according to the National Cancer Institute's (NCI) Surveillance, Epidemiology and End Results Program. It is estimated that 1 of every 9 women in the U.S. will develop breast cancer and the American Cancer Society estimates that 203,500 new cases of breast cancer will be diagnosed, with 40,000 deaths due to the disease occurring in the U.S. this year. The incidence of breast cancer varies between different countries, with a greater incidence in higher socioeconomic status groups. Incidence also increases with age, with approximately 80% of the cases afflicting women over the age of 50 (average age at diagnosis = 64 years). Breast cancer is not limited to women, although the incidence in men is markedly lower. It has been estimated that about 1500 new cases of male breast cancer will be diagnosed and 400 cases will result in death this year (4).

In addition to environmental factors, genetic factors appear to play a major role in the development of breast cancer and the risk is high in those individuals with a history of the disease among relatives. Several oncogenes have recently been linked to breast cancer. The tumor suppressor genes BRCA1 and BRCA2 localized on chromosome 17 and 13, respectively, have been linked to the development of several cancers including breast. The protooncogene HER2/neu localized on chromosome 17q21 is implicated in several types of cancers; approximately 20-30% of all breast cancers overexpress the HER2 gene and amplification or overexpression of HER2/neu correlates with poor prognosis. Mutation in the p53 tumor suppressor gene is the most common genetic

Scheme 2: Synthesis of Pipendoxifene



abnormality seen in cancer and up to 50% of all primary breast carcinomas have this mutation. Inflammatory breast cancer, the most deadly form of the disease, has been directly linked to the RhoC GTPase gene; this oncogene may also be involved in other aggressive forms of breast cancer. Another oncogene, GKLF, has also been implicated in breast cancer, with the gene overexpressed in about 70% of all breast carcinomas. In addition to oncogenes, a polymorphism of the transforming growth factor β_1 gene (TNF-β_1; C/C genotype at nucleotide 29) has been linked to breast cancer susceptibility in older Caucasian women (4-8).

Although surgery is the most common treatment for breast cancer, it is often performed in conjunction with radio- and/or chemotherapy. Breast cancer is hormonally dependent and some types which express the α or β estrogen receptor (ERα, ERβ) require a low level of circulating estrogen to thrive; withdrawal of estrogenic stimulation results in involution and shrinkage of this type of carcinoma. Thus, hormonal manipulation to block estrogen-stimulated growth can be an effective treatment against certain forms of breast cancer. Available therapies to reduce the detrimental effects of prolonged exposure to estrogen include antiestrogens (also called selective estrogen receptor modulators [SERMs]) which completely inhibit estrogen binding to ERα and/or ERβ, nonsteroidal SERMs which bind to ERα and/or ERβ exerting estrogen-agonist effects in some tissue (*e.g.*, bone, heart) and estrogen-antagonist effects in others (*e.g.*, breast, uterus), and, an alternative strategy, the selective estrogen enzyme modulators (SEEMs) that inhibit enzymes (*e.g.*, 17β-hydroxysteroid dehydrogenase,

Table I: In vitro *pharmacological profile of pipendoxifene and other selective estrogen receptor modulators (from Prous Science Integrity®).*

Compound	Estrogen receptor affinity[a] ERα	ERβ	Mitogenesis inhibition[b]	Gene transcription inhibition[c]
Arzoxifene	NA	NA	0.3-0.4 (23-25)	NA
Bazedoxifene	23 (2)	85 (2)	NA	3.70 (2)
Lasofoxifene	4.8 (20)	NA	0.05-0.4 (24, 26)	NA
Pipendoxifene	14 (2, 14)	40 (2)	0.21-0.70 (14, 15)	1.50 (2)
Raloxifene	2.0-4.0 (2, 21)	43 (2, 21)	0.20-7.5 (14, 15, 24, 27-31)	0.72 (2, 21)
Tamoxifen[d]	197 (14)	950 (22)	480-904 (14, 23, 27, 30)	NA

[a]Receptor affinities evaluated by displacement of [^{3}H]-estradiol from human ERα and ERβ receptors. [b]Inhibition of estradiol-induced mitogenesis of MCF-7 human breast adenocarcinoma cells. [c]Inhibition of estradiol-induced gene transcription evaluated using the MCF-7 ERE-tk-luciferase assay. [d]Tamoxifen included for comparative purposes. NA: data not available. References are in parentheses.

aromatase, estrone sulfate) involved in estrogen synthesis.

Tamoxifen is one of the oldest and most effective hormonal antiestrogens or first-generation SERMs with both estrogenic agonist and antagonist effects. Tamoxifen is generally well tolerated and has been shown to have particular efficacy in the treatment of ERα-positive metastatic breast cancers; the response rate to tamoxifen is about 30%. However, other treatments are still needed since an estimated 90% of women with metastatic cancer who respond to tamoxifen develop resistance to the agent within 1 year and other patients have inherent resistance to the drug. Tamoxifen has also been associated with adverse events such as endometrial cancer, gynecological symptoms, hot flashes and vascular complications (9, 10).

Several SERMs, including tamoxifen analogs, have been developed in the last decade. Although structurally related, SERMs have very distinct agonist and antagonist pharmacological profiles, possibly due to exertion of different conformational changes of the ER by each agent (11-13). Thus, the search continues for compounds with increasingly selective profiles.

A new 2-phenyl indole SERM, pipendoxifene (ERA-923) has been identified and shown to potently and competitively inhibit estrogen binding to both ERα and ERβ. Due to its excellent antiestrogenic preclinical profile and lack of uterotropic effects, pipendoxifene was selected for further development in the treatment of metastatic breast cancer.

Pharmacological Actions

In a cell-free *in vitro* assay assessing the ability to displace [^{3}H]-17β-estradiol binding in estrogen receptor ligand binding domain constructs, pipendoxifene showed affinity for both the human ERα (IC_{50} = 14 ± 10 nM) and ERβ (IC_{50} = 40 ± 24 nM), with a slight preference for ERα. Pipendoxifene was more potent than tamoxifen (IC_{50} = 197 ± 43 nM) in displacing 17β-estradiol from ERα. The agent was also shown to inhibit estrogen-regulated element activity and C3-promoter activity with IC_{50} values of 6.7 and 3.8 nM, respectively (2, 14, 15).

The functional estrogenic/antiestrogenic activity of pipendoxifene was examined in an MCF-7 cell (ERα-positive cell line) ERE-tk-luciferase transient transfection assay. Results showed that the agent did not stimulate transcriptional activity, indicating no agonist activity. However, potent antagonist activity in displacing 17β-estradiol (IC_{50} = 1.5 ± 0.4 nM) was observed.

Pipendoxifene inhibited estrogen-stimulated growth of MCF-7 cells (IC_{50} = 0.21 ± 0.16 nM) in a manner comparable to tamoxifen (IC_{50} = 0.20 ± 0.15 nM).Treatment with pipendoxifene was associated with cytostasis, inhibiting cells in the G_0/G_1 phase of the cell cycle. Proliferation of a human endometrial cell line (EnCa-101) and human ovarian carcinoma cells (BG-1) were also inhibited by pipendoxifene. Moreover, pipendoxifene was effective in inhibiting growth of a MCF-7 variant with inherent resistance to tamoxifen (10-fold) and 4-OH-tamoxifen (> 1000-fold), and a MCF-7 variant with acquired profound tamoxifen resistance remained partially susceptible to the agent (14-16).

The *in vitro* pharmacological profiles of pipendoxifene and other SERMs are shown in Table I.

Pipendoxifene (10 and 100 μg/rat = about 0.2 and 2 mg/kg) had no significant stimulatory effects on uterine endothelium in an immature rat uterine model in which rats were treated with the agent alone for 3 days s.c. However, the agent completely antagonized 17β-estradiol-stimulated uterine wet weight increases in this model. In contrast, raloxifene (10 and 100 μg/rat) significantly increased uterine wet weight. Pipendoxifene was also devoid of uterotropic activity in nude athymic mice treated orally with the agent alone once daily for 7 days. In contrast, both tamoxifen and droloxifene were uterotropic. Similarly, no increases in uterine wet weight were seen in athymic mice treated with pipendoxifene (10 mg/kg/day) for 22 days i.p. or 44 days p.o. while 10 mg/kg tamoxifen p.o. for 44 days increased uterine wet weight by 3-fold (2, 14).

Pipendoxifene was further shown to be devoid of proestrogenic uterine effects in estrogen-treated mice bearing EnCa-101 xenografts. In contrast to tamoxifen (2 or 20 mg/kg/day p.o.) which significantly stimulated tumor growth, 20 mg/kg/day pipendoxifene had no such effect and was antiestrogenic, causing a regression of

tumors; pipendoxifene at a dose 2 mg/kg had no agonist activity but did not affect estrogen-stimulated growth (14).

The efficacy of pipendoxifene (10 mg/kg/day p.o. starting when tumors were about 3-fold larger than at implantation) against 17β-estradiol-stimulated (1.7 or 0.72 mg slow release estradiol pellets implanted 1-7 days before MCF-7 implantation) growth of human breast carcinoma was shown *in vivo* in a mouse xenograft model. Treatment with the agent inhibited tumor growth by 88%; the minimum effective concentration for significant inhibition of tumor growth in this model was 3 mg/kg/day. The effects of pipendoxifene were concluded to be specific for estrogen-induced growth since mice bearing tumors devoid of ERα were susceptible to the agent. Pipendoxifene (10 mg/kg/day) was also effective when administered on day 1 postimplantation, where significant tumor growth inhibition of 28% was observed on day 14 as compared to estrogen-treated controls. Growth inhibition of 37-45% was sustained for the remainder of the experiment and persisted for at least 14 days after discontinuing pipendoxifene. In contrast, pipendoxifene was not effective when administered only for 2 weeks prior to tumor implantation (14).

In other experiments using tumor-bearing mice, pipendoxifene (10 and 20 mg/kg/day p.o.) was effective in inhibiting estradiol-stimulated growth of endometrial (EnCa-101) and ovarian (BG-1) tumors. Pipendoxifene (20 mg/kg/day p.o.) was particularly effective against BG-1 tumors, with inhibitory effects sustained for more than 20 days postdosing (14).

Clinical Studies

The safety and pharmacokinetics of pipendoxifene have been evaluated in 2 randomized, double-blind, placebo-controlled trials involving healthy postmenopausal women. The first study involved 46 subjects given a single pipendoxifene dose or placebo followed by a single higher dose after a 20-day washout period (1/5, 5/25, 25/50, 50/75, 75/100, 100/150, 150/200 and 200 mg p.o.). Pipendoxifene was well tolerated with only mild transient adverse events observed at all doses. No vaginal discharge or bleeding or changes in clotting parameters were observed with treatment. While the $t_{1/2}$ value was comparable for all doses (30 ± 16 h), apparent clearance increased with dose. It was suggested that bioavailability of the agent may decrease with increasing doses (17).

The second trial was a multiple-dose trial conducted in 50 subjects orally administered pipendoxifene (10, 50, 100, 150 or 200 mg once daily after an overnight fast except on day 14 when it was taken 10 min after a standard high-fat breakfast and on days 1 and 28 when subjects were fasted for 4 h postdosing) for 28 days. Pipendoxifene was safe and well tolerated. As with the first study, adverse events were mild, reversible and unrelated to dose. The most common adverse events associated with the agent included headache (28% *vs.* 30% in placebo), pain (23% *vs.* 10% in placebo) and hot flashes (20% *vs.* 20% in placebo) No clinically relevant changes in laboratory parameters or vaginal bleeding or discharge were observed. In addition, there was no increase in the incidence of ovarian cysts or significant changes in endometrial thickness as compared to placebo. Pharmacokinetic analysis revealed that the agent underwent extensive metabolism and enterohepatic recirculation. Clearance values increased with dose (~4-10.5 l/h/kg) but were similar on days 14 and 28 for each dose. Mean $AUC_{(0\text{-}24\ h)}$ for unconjugated pipendoxifene increased less than proportional with increasing dose in fasted and fed states. The $AUC_{(0\text{-}24\ h)}$ and C_{max} values for unconjugated pipendoxifene on day 14 (fed state) were significantly greater than those obtained on day 28 in groups given doses of 50 mg or higher. The mean terminal $t_{1/2}$ ranged from 15.8-27.3 h for all doses and steady-state plasma levels were achieved after about 4-5 days of dosing. The mean $t_{1/2}$ values for the 10, 50 and 100 mg were similar. However, mean $t_{1/2}$ values for the 150 and 200 mg doses were significantly different (15.8 and 26 h, respectively). A second peak in plasma concentrations was observed suggesting enterohepatic circulation. These secondary peaks were more marked in the fasted state as compared to the fed state. From these results it appears that a high-fat breakfast may increase absorption of the agent. Examination of markers for bone metabolism showed no differences in serum bone alkaline phosphatase, serum osteocalcin and urine free deoxypyridinoline between the pipendoxifene groups and placebo. In addition, total cholesterol, HDL, LDL and triglycerides were similar between placebo and treatment groups on days 14 and 28. Dosing with pipendoxifene for 28 days was concluded to be safe and well tolerated in postmenopausal women (17, 18).

A phase II trial of pipendoxifene in women with hormone-dependent metastatic breast cancer is currently under way and phase III trials are scheduled for the second half of 2002 (2, 14, 19).

Source

Wyeth Pharmaceuticals (US) in codevelopment with Ligand Pharmaceuticals, Inc. (US).

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