Maturitas 71 (2012) 194–198

Contents lists available at SciVerse ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

EMAS clinical guide: Selective estrogen receptor modulators for postmenopausal osteoporosis

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ARTICLE INFO

Article history:
Received 9 November 2011
Accepted 9 November 2011

Keywords:
Postmenopausal osteoporosis
Selective estrogen receptor modulators
Bazedoxifene
Lasofoxifene
Raloxifene
Tamoxifen

ABSTRACT

Osteoporosis and the resulting fractures are major public health issues as the world population is ageing. Various therapies such as bisphosphonates, strontium ranelate and more recently denosumab are available. This clinical guide provides the evidence for the clinical use of selective estrogen modulators (SERMs) in the management of osteoporosis in postmenopausal women.

1. Introduction

Osteoporosis and subsequent fractures have a major impact on morbidity and mortality worldwide [1].

Thus the World Health Organization has included fracture prevention in its list of public health priorities [2].

World-wide, osteoporotic fractures accounts for 0.83% of the global burden of non-communicable disease, and 1.75% of the global burden in Europe [3]. In Europe, osteoporotic fractures account for more Disability Adjusted Life Years (DALYs) lost than common cancers with the exception of lung cancer. For chronic musculo-skeletal disorders the DALYs lost in Europe due to osteoporosis (2.0 million) are less than for osteoarthritis (3.1 million) but greater than for rheumatoid arthritis (1.0 million). The economic burden is considerable and it has been estimated that the direct cost of osteoporotic fractures in Europe is about €36 billion [4]. Furthermore, in the absence of a significant treatment impact on the global burden of fractures, these costs are set to increase two-fold or more by 2050.

Various therapies such as bisphosphonates, strontium ranelate and more recently denomsumab are available [5,6]. However concerns have been raised regarding safety such as oesophageal cancer, osteonecrosis of the jaw (ONJ) and subtrochanteric fractures with bisphosphonates and venous thromboembolism with strontium ranelate [5,7]. This guidance aims to summarise the evidence on SERMs as the European Medicines Agency (EMA) has approved the use of bazedoxifene and lasofoxifene for the treatment of osteoporosis.

2. Selective estrogen receptor modulators

SERMs are chemically diverse compounds that lack the steroid structure of estrogens, but interact with estrogen receptors (ERS)

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doi:10.1016/j.maturitas.2011.11.010

as agonists or antagonists depending on the target tissue. The agonist and antagonist properties of SERMs derive from differentially expressed ERs, ligand-dependent receptor conformational changes, interactions with various coactivators and corepressors expressed and recruited in different tissues, and subsequent changes in gene transcription. Differential gene regulation with different SERMs ultimately contributes to the different cell- and tissue-specific activities of SERMs [8].

The early SERMs tamoxifen, toremifine and raloxifene were originally developed for the prevention and treatment of breast cancer and were subsequently found to conserve bone mass [8]. Tamoxifen has been used for several decades. Raloxifene is indicated for the treatment and prevention of osteoporosis in postmenopausal women in the United States and Europe. Toremifine will not be discussed further as data regarding osteoporosis are scant. Two new SERMs, bazedoxifene and lasofoxifene, are now licensed in Europe.

3. Tamoxifen

Tamoxifen is a triphenylethylene derivative with a particular affinity for estrogen receptors. While it has anti-estrogenic properties in the breast it acts as an agonist in some tissues such as the endometrium increasing the risk of cancer [8].

Tamoxifen is used as adjuvant treatment for node-positive and node-negative breast cancer to reduce risk of invasive breast cancer, and also to reduce breast cancer incidence in high-risk women [9,10]. A meta-analysis of 55 trials of 37,000 women demonstrated that the risk of breast cancer recurrence was significantly reduced by 18%, 25% and 42% following 1, 2, or 5 years, respectively, of adjuvant tamoxifen therapy compared with no treatment [11].

Ding and Field reviewed the effect of tamoxifen on bone health in postmenopausal women with early breast cancer and found that bone mineral density (BMD) was conserved at the spine and hip but not the wrist [12]. While there is no evidence that tamoxifen reduces the risk of fracture the incidence of fractures is lower in tamoxifen compared with aromatase inhibitor users [13]. Tamoxifen is not indicated for the prevention or treatment of postmenopausal osteoporosis.

4. Raloxifene

This benzothiophene was originally designed as a drug to treat breast cancer. Nevertheless, its clinical development focused afterwards on the prevention and treatment of postmenopausal osteoporosis and it became the first licensed SERM for this indication [8].

Raloxifene (RLX) is indicated for the prevention and treatment of osteoporosis in postmenopausal women in the United States and Europe [8]. Since raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer, in the United States, it is also indicated for reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and those at high risk for invasive breast cancer [8].

According to a meta-analysis including seven clinical studies, RLX in dose of 60 mg or 120/150 mg daily reduced the risk for vertebral fracture by 40% (RR, 0.60; 95% CI, 0.49–0.74) and 49% (RR, 0.51; 95% CI, 0.41–0.64) respectively [14]. It significantly reduced the risk of invasive breast cancer but only for estrogen receptor positive tumors (RR, 0.24; 95% CI, 0.15–0.40 [15].

Furthermore in a 5-year study of postmenopausal women ($n = 19{,}747$) at high risk of breast cancer, both raloxifene and tamoxifen were similarly effective in reducing the risk of invasive breast cancer [16]. However raloxifene had a significantly lower risk of endometrial hyperplasia, thromboembolic events, and cataracts than tamoxifen. An update of this study showed a reduced risk of endometrial cancer in raloxifene users [17]. With regard to cardiovascular events, raloxifene has no clear benefits on coronary heart disease and increases the risk of stroke and venous thromboembolism [18,19].

Raloxifene use has been associated with an increase in vasomotor symptoms, particularly hot flushes. A meta-analysis of the pooled adverse event data from all osteoporosis prevention trials reported a 7% increase in incidence of hot flushes using raloxifene (24.6%) vs. placebo (18.3%), although some RCTs did not observe this higher frequency or severity of vasomotor symptoms [20]. It has been reported that slow-dose escalation decrease the number of symptomatic patients when starting RLX [21].

Thus RLX 60 mg daily reduces the risk of vertebral but not nonvertebral fracture and its ability to reduce the risk of breast cancer without increasing the risk of endometrial cancer may be an advantage for some women.

5. New generation SERMs

5.1. Bazedoxifene

Bazedoxifene (BZA) is an indole-based third-generation SERM, with the phenyl rings serving as union receptor sites. It was developed for the prevention and treatment of postmenopausal osteoporosis [8].

5.1.1. Trial efficacy data

Bazedoxifene was evaluated in two phase III studies. In a 2-year prevention trial 1583 healthy postmenopausal women with low or normal BMD received daily doses of BZA of 10, 20, 40 mg; 60 mg of RLX or placebo, and all took 600 mg of elemental calcium daily [22]. All three doses of BZA and RLX were similarly effective at conserving BMD at the hip, lumbar spine, femoral trochanter and femoral neck. Within a six-month period, the three doses of BZA had already demonstrated a significant reduced BMD loss compared to placebo. The differences in mean percentage of BMD in the lumbar spine with respect to baseline at 24 months using 10, 20, and 40 mg BZA, vs. placebo, were $1.08 \pm 0.28\%$, $1.41 \pm 0.28\%$ and $1.49 \pm 0.28\%$, respectively (with a statistical significance of $p < 0.001$ for all of them).

A pivotal phase III clinical study was undertaken to evaluate the effectiveness and safety of BZA in preventing fractures in postmenopausal women with osteoporosis (55–85 years of age) [23]. Participants received daily treatment of BZA 20 mg ($n = 1886$) or 40 mg ($n = 1872$), RLX 60 mg ($n = 1849$) or placebo ($n = 1.885$), as well as a daily supplement of 1200 mg calcium and 400–800 IU of vitamin D. Among 6847 subjects in the intent-to-treat population, the incidence of new vertebral fractures was significantly lower ($p < 0.05$) with bazedoxifene 20 mg (2.3%), bazedoxifene 40 mg (2.5%), and raloxifene 60 mg (2.3%) compared with placebo (4.1%), with relative risk reductions of 42%, 37%, and 42%, respectively. The treatment effect was similar among subjects with or without prevalent vertebral fracture ($p = 0.89$ for treatment by baseline fracture status interaction). The incidence of nonvertebral fractures with bazedoxifene or raloxifene was not significantly different from placebo. In a post hoc analysis of a subgroup of women at higher fracture risk (femoral neck T-score ≤ -3.0 and/or ≥ 1 moderate or severe vertebral fracture or multiple mild vertebral fractures; $n = 1772$), bazedoxifene 20 mg showed a 50% and 44% reduction in nonvertebral fracture risk relative to placebo ($p = 0.02$) and raloxifene 60 mg ($p = 0.05$), respectively.

The 2-year extension included a total of 4216 women providing 5 year data [24]. The raloxifene arm was discontinued after

3 years; subjects receiving bazedoxifene 40 mg were transitioned to bazedoxifene 20 mg after 4 years. Five-year findings were reported for bazedoxifene 20 and 40/20 mg and placebo. At 5 years, the incidence of new vertebral fractures in the intent-to-treat population was significantly lower with bazedoxifene 20 mg (4.5%) and 40/20 mg (3.9%) versus placebo (6.8%; $p < 0.05$), with relative risk reductions of 35% and 40%, respectively. Non-vertebral fracture incidence was similar among groups. In a subgroup of higher-risk women ($n = 1324$; femoral neck T-score ≤ -3.0 and/or ≥ 1 moderate or severe or ≥ 2 mild vertebral fracture[s]), bazedoxifene 20 mg reduced non-vertebral fracture risk versus placebo (37%; $p = 0.06$); combined data for bazedoxifene 20 and 40/20 mg reached statistical significance (34% reduction; $p < 0.05$). After 7-years continuing benefit on vertebral fracture risk was still found [25].

A novel approach to hormone therapy is combing an estrogen with a SERM and this pairing is called "Tissue Selective Estrogen Complex (TSEC)". The rationale is to diminish hot flushes, treat vaginal atrophy and its symptoms, and prevent loss of bone mass, without stimulating the breast or endometrium. The BZA in combination with and conjugated estrogen (CE) in dosages of 0.45 or 0.625 mg significantly decreases vasomotor symptoms (26), improves vaginal symptoms [27] and increases bone mineral density in lumbar spine and hip [28]. Clearly this is a promising treatment for both vasomotor symptoms and osteoporosis prevention.

5.1.2. Safety data

The number of reported cardiac disorders and cerebrovascular events was equally low among all treatment groups up to 7 years [23–25]. While the general occurrence of pulmonary embolism and retinal vein thrombosis was increased in the treatment groups compared to placebo, this was not statistically significant [25,29,30]. However the risk of deep vein thrombosis was significantly increased after 3 years (RR 8 (CI, 1.01–64.25)) [25,29,30]. After 3, 5 and 7 years, there were no differences in breast cancer incidence between the different groups [25,29,30]. BZA has demonstrated a favourable endometrial profile over 5 years of therapy [30]. Compared with placebo, no increase in endometrial thickness of incidence of endometrial hyperplasia, or endometrial cancer was found compared with placebo [30], but low incidence of endometrial cancer ($p < 0.05$) was found in the BZA group versus placebo after 7 years [25]. There was no significant difference in the incidence of vaginal bleeding, or ovarian cysts between the groups up to 7 years [25,29,30].

The only adverse effects which increased particularly after years 3, 5 and 7 in the BZA groups vs. placebo were hot flushes ($p < 0.001$) and leg cramps ($p < 0.01$). The majority of adverse reactions occurring during the clinical trials were mild to moderate in severity and did not lead to discontinuation of therapy [25,26,30].

5.2. Lasofoxifene

Lasofoxifene, a naphthalene derivative, third-generation SERMs with better oral bioavailability than other compounds, and, was developed for osteoporosis prevention and treatment in postmenopausal women [31].

The affinity of lasofoxifene to estrogen receptor (ER) alpha is similar to that of estradiol and higher than that of either raloxifene or tamoxifen [31,32].

5.2.1. Trial efficacy data

Two phase III clinical trials have been conducted: the Osteoporosis Prevention and Lipid Lowering (OPAL) studies and the Postmenopausal Evaluation and Risk Reduction with Lasofoxifene (PEARL) study. In the OPAL studies 1907 non-osteoporotic postmenopausal women aged 40–75 were randomized to lasofoxifene 0.0025, 0.25, or 0.5 mg/day, or to placebo for 2 years. In year 2, lumbar BMD increased by 1.5, 2, 3, and 2.3% in lasofoxifene 0.025, 0.25, and 0.5 treatment groups, respectively vs. a decrease of 0.7% in placebo users. Vaginal atrophy (evaluated by vaginal pH or by an increase in the percentages of intermediate and superficial vaginal cells) was improved after 1 and 2 years of treatment, using all doses of lasofoxifene, as compared to placebo [33,34].

The pivotal (PEARL) trial randomized 8556 women aged 59–80—with a BMD T score of −2.5 or less at the femoral neck or spine, to receive a daily dose of lasofoxifene (0.25 mg or 0.5 mg) or placebo 5 years. Lasofoxifene at a dose of 0.5 mg/day, as compared with placebo, was associated with reduced risks of vertebral fracture (13.1 cases vs. 22.4 cases per 1000 person-years; hazard ratio, 0.58; 95% confidence interval [CI], 0.47–0.70), nonvertebral fracture (18.7 vs. 24.5 cases per 1000 person-years; hazard ratio, 0.76; 95% CI, 0.64–0.91). Lasofoxifene administration was associated with significant reductions in ER-positive breast cancer (0.3 vs. 1.7 cases per 1000 person-years; hazard ratio, 0.19; 95% CI, 0.07–0.56), coronary heart disease events (5.1 vs. 7.5 cases per 1000 person-years; hazard ratio, 0.68; 95% CI, 0.50–0.93), and stroke (2.5 vs. 3.9 cases per 1000 person-years; hazard ratio, 0.64; 95% CI, 0.41–0.99). Lasofoxifene at a dose of 0.25 mg/day, as compared with placebo, was associated with reduced risks of vertebral fracture (16.0 vs. 22.4 cases per 1000 person-years; hazard ratio, 0.69; 95% CI, 0.57–0.83) and stroke (2.4 vs. 3.9 cases per 1000 person-years; hazard ratio, 0.61; 95% CI, 0.39–0.96) [35,36].

5.2.2. Safety data

Both the lower and higher doses, as compared with placebo, were associated with an increase in venous thromboembolic events (3.8 and 2.9 cases vs. 1.4 cases per 1000 person-years; hazard ratios, 2.67 [95% CI, 1.55–4.58] and 2.06 [95% CI, 1.17–3.60], respectively), but there was no evidence of an increase in the incidence of pulmonary embolism.

Lasofoxifene treatment does not adversely affect the pelvic floor and was not associated with an increase in surgery for uterine prolapse. The endometrial effects of lasofoxifene have been evaluated and no increase in endometrial hyperplasia, atypia, or cancer was found, although mean endometrial thickness, showed a marginal but statistically significant increase due to tissue hydration and cystic echotexture on ultrasound. Endometrial cancer occurred in three women in the placebo group, two women in the lower-dose lasofoxifene group, and two women in the higher-dose lasofoxifene group.

A nested case–control study of 49 incident breast cancer case patients and 156 unaffected control subjects from the PEARL trial was performed to evaluate treatment effects on risk of total and ER-positive (ER+) invasive breast cancer by baseline serum estradiol and sex hormone-binding globulin levels using logistic regression models. Compared with placebo, 0.5 mg of lasofoxifene statistically significantly reduced the risk of total breast cancer by 79% (hazard ratio = 0.21; 95% confidence interval [CI] = 0.08–0.55) and ER+ invasive breast cancer by 83% (hazard ratio = 0.17; 95% CI = 0.05–0.57). The effects of 0.5 mg of lasofoxifene on total breast cancer were similar regardless of Gail score, whereas the effects were markedly stronger for women with baseline estradiol levels greater than the median (odds ratio = 0.11; 95% CI = 0.02–0.51) vs. those with levels less than the median (odds ratio = 0.78; 95% CI = 0.16–3.79; P(interaction) = .04) [36].

Lasofoxifene increased hot flushes and leg cramps using both doses (0.25 and 0.5 mg) ($p < 0.001$ and $p < 0.001$) [35]. Rates of death per 1000 person-years were 5.1 in the placebo group and 5.7 in the higher-dose lasofoxifene group (0.5 mg/day), the dose that is intended for clinical use [35].

6. Conclusion

Differential gene regulation with individual SERMs leads to the different cell- and tissue-specific activities of SERMs [8]. Thus use of a particular SERM requires a case-by-case risk-benefit analysis for each woman.

Tamoxifen is the front-line agent for the treatment and prevention of breast cancer. However the lack of fracture data and its endometrial stimulatory effects, precludes its use in osteoporosis prevention. On the other hand, raloxifene reduces the risk of breast cancer and osteoporotic fracture without endometrial stimulation.

The EMA approved indication for BZA in the treatment of osteoporosis in postmenopausal women at increased risk of fracture. These new SERMs points to a greater anti-fracture potential than raloxifene with positive breast, endometrium, coronary heart disease and stroke safety profiles over seven years. Currently BZA is available in Spain, Switzerland, Italy, Ireland and Japan and it is anticipated will be launched soon in other countries.

Lasofoxifene was approved in Europe in 2009 for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. FDA (Food and Drug Administration) approval has not been granted. Safety findings noted by the FDA included increased incidence of uterine diagnostic procedures, increased incidence of VTE, and a small, but significant increase in all-cause mortality with the 0.25 mg, but not the 0.5 mg, dose [37].

The decision, of when to begin and what type of treatment to use, should be based on the need to reduce fracture risk. All treatments including SERMS should include recommendations for a healthy life style and adequate calcium and vitamin D intake. Additional benefits of different agents (i.e. climacteric symptom improvement with estrogens, breast cancer prevention for SERMS) must be considered when selecting the anti-osteoporosis drug. Furthermore what agent is used (estrogen, SERM, bisphosphonates) may vary over a woman's life time.

Competing interests

Santiago Palacios has been a symposium speaker or advisory board member for Servier, Pfizer, Pierre-Fabre, Bayer Schering Pharma, Lilly, Daiichi-Sankyo, Roche, Warner Chilcott, Amgen, Arkopharma and Boehringer-Ingelheim; and received research grants and/or consulting fees from Pfizer, Servier, Lilly, Daiichi-Sankyo, Amgen, Arkochim and Bayer Schering Pharma. Serge Rozenberg has been an advisory board member for Pfizer.

Provenance and peer review

EMAS clinical guide.

Acknowledgements

S.P. and S.R. prepared the initial draft which was circulated to all EMAS board members for comment and approval, production was coordinated by MR.

References

[1] Leboime A, Confavreux CB, Mehsen N, Paccou J, David C, Roux C. Osteoporosis and mortality. Joint Bone Spine 2010;77(December (Suppl 2)):S107–12.
[2] World Health Organization. http://www.who.int/nutrition/topics/5_population_nutrient/en/index25.html [accessed 08.11.11].
[3] Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int 2006;17(12):1726–33.
[4] Kanis JA, Johnell O. Requirements for DXA for the management of osteoporosis in Europe. Osteoporos Int 2005;16:229–38.
[5] Rees M, Stevenson J, Hope S, Palacios S, Rozenberg S. Management of the menopause. 5th ed. Royal Society of Medicine Press; 2009.
[6] Lewiecki EM. Treatment of osteoporosis with denosumab. Maturitas 2010;66(June (2)):182–6.
[7] Rozenberg S, Dutton S. Bisphosphonates and oesophageal cancer risk: where are we now? Maturitas 2011;68(February (2)):106–8.
[8] Pickar JH, MacNeil T, Ohleth K. SERMs: progress and future perspectives. Maturitas 2010;67(October (2)):129–38.
[9] Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90:1371–88.
[10] Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 2005;97:1652–62.
[11] Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet 1998;351:1451–67.
[12] Ding H, Field TS. Bone health in postmenopausal women with early breast cancer: how protective is tamoxifen? Cancer Treat Rev 2007;33(October (6)):506–13.
[13] Rabaglio M, Sun Z, Price KN, et al. Bone fractures among postmenopausal patients with endocrine-responsive early breast cancer treated with 5 years of letrozole or tamoxifen in the BIG 1-98 trial. Ann Oncol 2009;20(September (9)):1489–98.
[14] Seeman E, Crans GG, Diez-Perez A, Pinette KV, Delmas PD. Anti-vertebral fracture efficacy of raloxifene: a meta-analysis. Osteoporos Int 2006;17(February (2)):313–6.
[15] Siris ES, Harris ST, Eastell R, et al. Skeletal effects of raloxifene after 8 years: results from the continuing outcomes relevant to Evista (CORE) study. J Bone Miner Res 2005;20(September (9)):1514–24.
[16] Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs. raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA 2006;295(23):2727–41.
[17] Vogel VG, Costantino JP, Wickerham DL, et al. National Surgical Adjuvant Breast and Bowel Project, Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: preventing breast cancer. Cancer Prev Res (Phila) 2010;3(June (6)):696–706.
[18] Barrett-Connor E, Mosca L, Collins P, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med 2006;355:125–37.
[19] Collins P, Mosca L, Geiger MJ, et al. Effects of the selective estrogen receptor modulator raloxifene on coronary outcomes in the Raloxifene Use for The Heart trial: results of subgroup analyses by age and other factors. Circulation 2009;119(7):922–30.
[20] Davies GC, Huster WJ, Lu Y, Plouffe L, Lakshmanan M. Adverse events reported by postmenopausal women in controlled trials with raloxifene. Obstet Gynecol 1999;93:558–65.
[21] Palacios S, Farias ML, Luebbert H, et al. Raloxifene is not associated with biologically relevant changes in hot flushes in postmenopausal women for whom therapy is appropriate. Am J Obstet Gynecol 2004;191(July (1)):121–31.
[22] Miller PD, Chines AA, Christiansen C, et al. Effects of bazedoxifene on BMD and bone turnover in postmenopausal women: 2-yr results of a randomized, double-blind, placebo-, and active-controlled study. J Bone Miner Res 2008;23:525–35.
[23] Silverman SL, Christiansen C, Genant HK, et al. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo- and active-controlled clinical trial. J Bone Miner Res 2008;23:1923–34.
[24] Silverman SL, Chines AA, Kendler DL, et al. Sustained efficacy and safety of bazedoxifene in preventing fractures in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled study. Osteoporos Int 2011 [Epub ahead of print].
[25] Palacios S, Silverman S, Levira A, Pallay A, Kaufman J, Brown J, et al. Long-term efficacy and safety of bazedoxifene in postmenopausal women with osteoporosis: results of a 7-year, randomized, placebo-controlled study. Presented at: 13th International Menopause Society World Congress on Menopause, June 8–11, 2011. Rome, Italy [Abstract 973].
[26] Lobo RA, Pinkerton JV, Gass ML, et al. Evaluation of bazedoxifene/conjugated estrogens for the treatment of menopausal symptoms and effects on metabolic parameters and overall safety profile. Fertil Steril 2009;92(September (3)):1025–38.
[27] Kagan R, Williams RS, Pan K, Mirkin S, Pickar JH. A randomized, placebo- and active-controlled trial of bazedoxifene/conjugated estrogens for treatment of moderate to severe vulvar/vaginal atrophy in postmenopausal women. Menopause 2010;17(March (2)):281–9.
[28] Lindsay R, Gallagher JC, Kagan R, Pickar JH, Constantine G. Efficacy of tissue-selective estrogen complex of bazedoxifene/conjugated estrogens for osteoporosis prevention in at-risk postmenopausal women. Fertil Steril 2009;92(September (3)):1045–52.
[29] Christiansen C, Chesnut 3rd CH, Adachi JD, et al. Safety of bazedoxifene in a randomized, double-blind, placebo- and active-controlled phase 3 study of postmenopausal women with osteoporosis. BMC Musculoskelet Disord 2010;11:130.
[30] De Villiers TJ, Chines AA, Palacios S, et al. Safety and tolerability of bazedoxifene in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled phase 3 trial. Osteoporos Int 2011;22(February (2)):567–76.
[31] Rosati RL, Da Silva Jardine P, Cameron KO, et al. Discovery and preclinical pharmacology of a novel, potent, non-steroidal estrogen receptor

agonist/antagonist, CP-336156, a diaryltetrahydronaphthalene. J Med Chem 1998;41(16):2928–31.
[32] Ke HZ, Paralkar VM, Grasser WA, et al. Effects of CP-336,156, a new, nonsteroidal estrogen agonist/antagonist, on bone, serum cholesterol, uterus and body composition in rat models. Endocrinology 1998;139(April (4)):2068–76.
[33] FABLYN® (lasofoxifene tartrate). 0.5 mg tablets, NDA22-242, Reproductive Health Drugs Advisory Committee Briefing Document. Available from: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-829 4381b1-02-Pfizer.pdf; 2008 [accessed on 25.02.11].
[34] Fablyn® (lasofoxifene tartrate). Summary of product characteristics. Pfizer. Final Summary Minutes, Advisory Committee for Reproductive Health Drugs Meeting. Available from: http://www.fda.gov/ohrms/dockets/ac/08/minutes/2008-4381m1-final.pdf; 2008 [accessed on 25.03.11].
[35] Cummings SR, Ensrud K, Delmas PD, et al. Lasofoxifene in postmenopausal women with osteoporosis. N Engl J Med 2010;362(8):686–96.
[36] LaCroix AZ, Powles T, Osborne CK, et al. Breast cancer incidence in the randomized PEARL trial of lasofoxifene in postmenopausal osteoporotic women. J Natl Cancer Inst 2010;102(22):1706–15.
[37] Final Summary Minutes, Advisory Committee for Reproductive Health Drugs Meeting. Available from: http://www.fda.gov/ohrms/dockets/ac/08/minutes/2008-4381m1-final.pdf; 2008 [accessed on 25.03.11].