EMAS clinical guide: Selective estrogen receptor modulators for postmenopausal osteoporosis

Santiago Palacios a,–h, Mark Brincat b, C. Tamer Erel c, Marco Gambacciani d, Irene Lambrinoudaki e, Mette H. Moen f, g, Karin Schenck-Gustafsson h, Florence Tremolieres i, Svetlana Vujovic j, Margaret Rees k, Serge Rozenberg l

a Palacios Institute of Woman's Health Antonio Acuna, 9, 28009 Madrid, Spain
b Department of Obstetrics and Gynaecology, Mater Dei Hospital, B’Kara Naxxar, Malta
c Department of Obstetrics and Gynecology, Istanbul University, Cerrahpasa School of Medicine, Valikonagi Cad. No. 93/4, Nisantasi 34365, Istanbul, Turkey
d University of Pisa, Department of Obstetrics and Gynecology, Via Roma 67, 56100 Pisa, Italy
e 2nd Department of Obstetrics and Gynecology, University of Athens, Aretaio Hospital, GR-11528 Athens, Greece
f Department of Laboratory Medicine, Children’s and Women's Health, Faculty of Medicine, Norwegian University of Science and Technology, NO-7491 Trondheim, Norway
g Department of Obstetrics and Gynecology, St. Olavs Hospital, Trondheim University Hospital, NO-7006 Trondheim, Norway
h Department of Medicine, Cardiology Unit and Head Centre for Gender Medicine, Karolinska Institutet and Karolinska University Hospital, Thorax N3:06, SE 17176 Stockholm, Sweden
i Menopause and Metabolic Bone Disease Unit, Hôpital Paule de Viguier, F-31059 Toulouse Cedex 09, France
j Institute of Endocrinology, Clinical Center of Serbia, Belgrade School of Medicine, Dr. Subotica 13, 11000 Beograd, Serbia
k Women’s Centre, John Radcliffe Hospital, Oxford OX3 9DU, UK
l Department of Obstetrics and Gynecology, CHU Saint Pierre, Université Libre de Bruxelles, 1000 Brussels, Belgium

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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.

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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 denosumab 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)
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, toremifene 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. Toremifene 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 non-vertebral 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 ± 0.28%, 1.41 ± 0.28% and 1.49 ± 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 = 1885), 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 (2.3%), 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 5year 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 fractures), 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 ectotexture 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) = 0.4) [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].
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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 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.

Lasoxifene 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 lifestyle 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, Daichi-Sankyo, Roche, Warner Chilcott, Amgen, Arkopharma and Boehringer-Ingelheim; and received research grants and/or consulting fees from Pfizer, Servier, Lilly, Daichi-Sankyo, Amgen, Arkohim and Bayer Schering Pharma. Serge Rozenberg has been an advisory board member for Pfizer.

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