Bazedoxifene: a new selective estrogen-receptor modulator for postmenopausal osteoporosis

Bazedoxifene acetate (WAY-140424; TSE-424) is an oral, nonsteroidal, indole-based selective estrogen-receptor modulator that is being clinically evaluated as a monotherapy for the prevention and treatment of osteoporosis and in combination with conjugated estrogens for the treatment of menopausal symptoms and prevention of osteoporosis. Developed by Wyeth (now Pfizer) Pharmaceuticals (NJ, USA), it is undergoing regulatory review for clinical use under the trade name Viviant™ by the US FDA. Bazedoxifene is currently marketed in Switzerland, Spain, Italy, Germany, Ireland and Japan. Its brand names in the EU and Japan are Conbriza® and Viviant™, respectively. In the EU, Conbriza is indicated for the treatment of postmenopausal osteoporosis in women at increased risk of fracture. Bazedoxifene reduces vertebral fractures in postmenopausal osteoporotic women, and nonvertebral fractures in a subgroup of postmenopausal osteoporotic women at higher risk. This review describes the mechanism of action and summarizes the clinical experience with bazedoxifene. Current evidence indicates that bazedoxifene is effective and safe for the treatment of postmenopausal osteoporosis.

KEYWORDS: bazedoxifene ■ fracture ■ osteoporosis ■ SERMs

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Osteoporosis is a global public health problem that is estimated to affect more than 200 million people worldwide. The disease affects one in three postmenopausal women and one in five men aged above 65 years. According to the WHO, osteoporosis is the cause of over 8.9 million fractures globally each year [1]. The combined lifetime risk for hip, spine and forearm fracture has been estimated to be approximately 40%, similar to that for coronary artery disease. By 2050, the cost of treating hip fracture alone in the USA is projected to be US$130 billion. In addition to this major burden on the health economy, hip fracture is associated with a mortality rate of 20–50% within the first year of occurrence. Although the age-adjusted fracture rates have leveled off in North America and Europe, there is a rising trend in most parts of Asia. Rapid aging and changing lifestyle habits of the population mean that most fractures in Asia are expected to occur in 50 years' time. In view of the major consequence of osteoporotic fractures, early prevention and treatment of individuals at risk remains an important goal throughout the world in the management of osteoporosis.

Overview of the market

Bone loss in postmenopausal women occurs as a result of lost estrogenic inhibition of osteoclastic bone resorption. Estrogen therapy or estrogen–progestin therapy, namely hormone replacement therapy, has been used extensively in postmenopausal women for both prevention and treatment of osteoporosis. However, the significant increase in incidences of breast cancer, stroke, heart attack and venous thromboembolism with estrogen–progestin therapy and the significant increase in the incidence of stroke with estrogen therapy outweighed the benefit of fracture risk reduction in older postmenopausal women [2]. Although other treatments for osteoporosis are available (bisphosphonates, RANKL inhibitor, parathyroid hormone, calcitonin and strontium ranelate), the development of agents that can mimic the action of estrogens in decreasing the rate of bone turnover and preserve or increase bone mass without the side effects of hormone replacement therapy would be preferable.

Selective estrogen-receptor modulators (SERMs) are nonsteroidal estrogen-like molecules that bind to the estrogen receptor (ER) α and β. Each SERM presents diverse clinical effects in response to the conformational changes following formation of a distinct ER–SERM ligand complex. They demonstrate variable agonist and antagonist activity that is dependent on the genes being regulated and occurs on a tissue-by-tissue basis (i.e., a tissue-selective response). An ideal SERM would possess agonistic ER action on bone with an associated reduced fracture risk and beneficial effects on lipoprotein cholesterols

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with decreased cardiovascular risks. It would have no stimulatory action on uterine endometrium or breast tissue. Positive effects in the CNS and vagina, with fewer hot flushes and the maintenance of vaginal secretion, would provide further benefits.

At present, two SERMs are available for clinical use: tamoxifen, a triphenylethylene approved for the treatment of breast cancer, and raloxifene, a benzothiophene approved for the prevention and treatment of postmenopausal osteoporosis and the prevention of breast cancer.

Introduction to the compound

Bazedoxifene acetate (WAY-140424; TSE-424) is an oral, nonsteroidal, indole-based SERM being developed for the prevention and treatment of osteoporosis. It is classified as a third-generation SERM and has the chemical name 1H-indo-5-ol,1-[[4-[2(hexahydro-1H-azepin-1-yl)ethoxy]methyl]2-(-4-hydroxyphenyl)-3-methyl] acetic acid [3]. The core binding domain consists of a 2-phenyl-3-methyl indole and a hexamethylenamine ring at the side chain affecter region.

Preclinical studies with bazedoxifene have demonstrated estrogen agonist effects on the skeleton and lipid metabolism but not on breast and uterine endometrium. Phase III clinical studies have shown favorable effects on the skeleton without stimulation of endometrium and breast: bone loss in postmenopausal women without osteoporosis is prevented and vertebral fractures in women with postmenopausal osteoporosis reduced. In women at high risk of fracture with multiple risk factors, bazedoxifene reduces non-vertebral fracture risk in *post hoc* analysis. Clinical trials with bazedoxifene have shown beneficial effects on bone mineral density and bone turnover markers with little or no stimulation of breast and endometrium.

Pharmacodynamics, pharmacokinetics & metabolism

Bazedoxifene binds to both ERα and ERβ, with a slightly higher affinity for ERα. The dissociation constant for ERα is approximately equal to 0.1 nM and for ERβ is 0.3 nM. The IC50 (i.e., inhibitory concentration required to compete 50% of 17β -estradiol [E2] off the estrogen receptor) for bazedoxifene is 23 ± 15 and 85 ± 59 nM for ERα and ERβ, respectively, compared with 4 ± 3 and 43 ± 13 nM, respectively, for raloxifene [3].

The oral bioavailability of bazedoxifene has been evaluated in 18 healthy postmenopausal women under fasting conditions. The absolute bioavailability of both tablet and capsule formulations is the same at approximately 6.2%, threefold higher than that of raloxifene [4]. To determine the pharmacokinetics, multiple oral doses of 5, 20 and 40 mg were administered to postmenopausal women in a crossover manner for 14 days. The maximum plasma concentration of bazedoxifene was achieved 1–2 h following administration. The elimination half-life was 28 h without accumulation. More than 99% of the compound was protein bound and a steady-state plasma concentration was achieved by day 7 of oral administration. When administration was extended to 30 days at various doses from 1 to 80 mg, plasma concentration increased in a linear fashion with steady-state achieved by day 14 [5].

The metabolic disposition of bazedoxifene was evaluated in six healthy postmenopausal women by evaluation of blood, urine and feces following administration of a single 20-mg oral dose of 14C-bazedoxifene [6]. Bazedoxifene was mainly excreted in the feces (84.7%), with only a minute amount excreted in the urine (0.81%). Glucuronidation is the major metabolic pathway, as the major metabolite is bazedoxifene-5-glucuronide. Little or no CYP450-mediated metabolism was found.

Preclinical data

Uterus

E2 stimulates the uterine endometrium and causes endometrial hyperplasia and cancer. The action of bazedoxifene on the uterus was evaluated with an immature rat model by assessing uterine wet weight [7,8]. At a dose of 0.5 mg/kg, bazedoxifene increased uterine wet weight by 35%; nonetheless, a dose of 5 mg/kg resulted in no significant difference in weight compared with placebo. Although the 0.5 mg/kg dose of bazedoxifene increased uterine wet weight, which is consistent with that seen with raloxifene, no luminal epithelial cell hypertrophy or hyperplasia, myometrial hypertrophy, or luminal distention was noted. These results show that the increased uterine weight was not accompanied by hypertrophy or hyperplasia. Overall, bazedoxifene exhibits a small stimulatory effect (at low doses) on rat uterine wet weight without detectable histological changes.

Breast

E2 stimulates the breast, exhibited by increased ductal branching with minimal end-bud cell proliferation, but has been associated with an increased risk of breast cancer. Bazedoxifene has no stimulatory effect on MCF-7 human breast tumor cell line proliferation [8,9]. In the presence

of E2, bazedoxifene dose-dependently inhibited E2-induced MCF-7 cellular proliferation with an IC50 value of 3.7 ± 1.6 nM [7]. In an *in vivo* mouse model, bazedoxifene and raloxifene did not stimulate end-bud formation. Both bazedoxifene and raloxifene were nevertheless able to inhibit E2-induced end-bud formation [10]. These data suggest that in breast tissue, bazedoxifene, like raloxifene, acts as an antagonist to inhibit the action of E2.

Bone

The effect of bazedoxifene on bone mineral density (BMD), bone morphometry and compressive strength has been evaluated in an ovariectomy (OVX) osteopenia rat model. After 6 weeks of treatment at a dose of 0.1–3.0 mg/kg/day bazedoxifene produced a dose-dependent increase in BMD and vertebral compressive strength, with the greatest effect being seen with a dose of 3.0 mg/kg/day [10]. Bone quality at the proximal tibia was maintained and correlated with the increases in BMD and compressive force data. In another study using the OVX monkey, bone densitometry and histomorphometric indices in cancellous and cortical bone revealed that bazedoxifene treatment for 18 months at doses up to 25 mg/kg/day protected against OVX-induced bone loss [11].

In a study using OVX mice, animals received bazedoxifene 0.3 mg/kg/day, raloxifene 3 mg/kg/day, lasofoxifene 0.1 mg/kg/day and risedronate 1 mg/kg/day, together with subcutaneous human parathyroid hormone 10 µg/kg/day for 4 weeks. Total and trabecular BMD were 3–10% higher in all combined treatment groups than in the human parathyroid hormone-monotherapy group. No significant difference was detected among the three SERMs.

Vasomotor

Hot flushes and vasomotor reactivity regulation is a common concern when using SERMs: hot flushes occur in postmenopausal women treated with raloxifene [12]. To mimic this topical rise in temperature, a morphine-addicted rat model was used by injecting naloxone into the tail vein to induce a rise in tail temperature [13]. E2, but not raloxifene, inhibited this temperature rise. Bazedoxifene at a dose needed to protect bone (0.3 mg/kg/day) has not been shown to inhibit or exacerbate the naloxone-induced temperature increase. Bazedoxifene functions as a potent ERα antagonist on ovarian, hepatic and neuronal cell lines cotreated with E2, but by itself does not activate the ER in these cells [3,8,14]. Overall, the preclinical data indicate that bazedoxifene may represent a promising new therapy for postmenopausal osteoporosis. In comparison with SERMs currently available in clinical practice, it demonstrates fewer uterine and vasomotor effects.

Lipid

In the 6-week OVX rat osteopenia model used to evaluate the skeletal effect of bazedoxifene, total cholesterol level was significantly reduced after 6 weeks of treatment with 0.3 mg/kg/day. This dose was approximately one-tenth the dose of raloxifene required to achieve the same effect. No further reduction in cholesterol level was seen with higher doses of bazedoxifene [11].

Phase I clinical studies

In addition to pharmacological properties, the first human study of bazedoxifene also evaluated biochemical markers of bone resorption and formation, coagulation parameters, lipid profile and vasomotor symptoms in response to bazedoxifene at a dose of 1–80 mg daily for 30 days [15]. The bone resorption marker collagen C-link N-telopeptide was reduced by 21% from baseline and fibrinogen was decreased by 19%. There was no increase in vasomotor symptoms and no adverse response in terms of blood biochemistry, endometrial thickness and ovarian volume at any therapeutic dose [5].

Phase II studies

Uterus

The effect of bazedoxifene on uterine endometrium was evaluated in a randomized active, placebo-controlled clinical trial of 497 postmenopausal women with an intact uterus. The subjects were randomized to either bazedoxifene 2.5, 5, 10 or 20 mg daily, an active control treatment of a combination of estrogen–progestin or placebo for 6 months [16]. All subjects received 600 mg of calcium daily. No difference in endometrial thickness was found between the bazedoxifene and placebo groups, whereas a slight but significant thickening of the endometrium was seen in the estrogen–progestin group. An extension study that involved 195 women treated with bazedoxifene 20, 30 and 40 mg daily or placebo, revealed that endometrial thickness was significantly reduced in women given bazedoxifene 30 and 40 mg ($p < 0.001$ vs placebo) [16]. None of the endometrial biopsies showed endometrial hyperplasia. These results suggest that at the higher doses of 30 and 40 mg, bazedoxifene inhibits endometrial stimulation, an effect not previously observed with other SERMs.

Skeleton

The effect of bazedoxifene on bone turnover and metabolism was evaluated in 294 postmenopausal Caucasian women randomized to receive bazedoxifene 5, 10 or 20 mg daily, raloxifene 60 mg daily or placebo for 3 months. All subjects received calcium supplementation of 600 mg/day [16]. Significant reductions in bone turnover markers were seen at the lowest dose of 5 mg ($p < 0.05$ vs placebo) and with raloxifene. A dose-dependent reduction in bone turnover markers was observed with bazedoxifene, with the greatest effect noted at higher doses. In another clinical study when participants were given bazedoxifene 20 or 40 mg, bone turnover was decreased by 20–25%, with no occurrence of endometrial hyperplasia [3,16].

In a randomized, double-blind, Phase II study to determine the effect of bazedoxifene versus placebo on lumbar spine BMD, 429 Japanese women with postmenopausal osteoporosis were randomized to bazedoxifene 20 or 40 mg daily or placebo for 2 years [17]. All subjects received daily supplementation of calcium 600 mg and vitamin D 400 IU. At 2 years, the mean percentage changes from baseline in lumbar spine BMD were significantly greater with bazedoxifene 20 and 40 mg (2.43 and 2.74%, respectively) than with placebo (-0.65%; $p < 0.001$ for both). There was no difference in spine BMD response between bazedoxifene 20 and 40 mg. A significant increase in spine BMD was observed as early as 6 months following commencement of bazedoxifene treatment, an effect that was maintained throughout the treatment period. Similar increase in BMD was observed at the femoral neck and total hip region, with no difference between bazedoxifene 20 and 40 mg. The study also addressed other secondary end points, including markers of bone turnover and incidence of osteoporotic fractures. Relative to placebo, bazedoxifene 20 and 40 mg significantly reduced the levels of serum C-telopeptide, N-telopeptide, osteocalcin and urinary N-telopeptide throughout the study and significant changes were detectable as early as 12 weeks ($p < 0.05$ for all). The incidence of new vertebral fractures with bazedoxifene 20 and 40 mg and placebo was 3.8, 2.4 and 4.7%, respectively, whereas the incidence of new nonvertebral fractures was 3.8, 2.4 and 3.1%, respectively.

Breast

The action of bazedoxifene on breast stimulation and breast pain was assessed in 351 postmenopausal women. Participants were randomized into six groups: bazedoxifene 2.5, 5, 10 or 20 mg, conjugated estrogen/medroxyprogesterone acetate combination or placebo [18]. The incidence of breast pain was recorded daily by the participants using diary cards and was highest in the conjugated estrogen/medroxyprogesterone acetate group. Bazedoxifene at any of the doses did not increase breast pain compared with placebo. Based on this observation, an extension study to evaluate the efficacy of bazedoxifene on breast stimulation recruited 236 participants who were randomized to bazedoxifene 20 or 40 mg or placebo. Similar results were observed, with a significantly lower incidence of breast pain with bazedoxifene 40 mg ($p < 0.05$ vs placebo); no significant effect was seen with the 20-mg dose. This study demonstrated that at a higher dose, bazedoxifene has an antagonistic effect on breast tissue.

Vasomotor effects

Further to the observation of an increased incidence of hot flushes with bazedoxifene and raloxifene compared with placebo in some studies, a 3-month, multicenter, randomized, double-blind, placebo- and active-controlled Phase II study was conducted to evaluate the vasomotor effects of bazedoxifene in nonflushing postmenopausal women [19]. Among the 487 subjects (mean age: 57.5 years) included in the intention-to-treat analysis, hot flushes were reported in 25.5% of placebo-treated subjects at the end of the 84-week study period. The incidence of hot flushes with bazedoxifene 5, 10 and 20 mg, and raloxifene 60 mg was 26, 33.7, 27.6 and 21.4%, respectively; none of the active treatment group was statistically different to placebo. There was no difference in the mean number and severity of hot flushes between the bazedoxifene and placebo groups.

Phase III clinical study

The efficacy and safety of bazedoxifene in the prevention of postmenopausal osteoporosis was determined in a 2-year, Phase III, multicenter, double-blind, randomized, active- and placebo-controlled study of 1583 postmenopausal women [20,21]. Subjects were healthy women aged 45 years and above (mean age: 57.6 years), who were at least 1 year postmenopausal, with lumbar spine or femoral neck BMD within the osteopenic range (T score between -1.0 and -2.5) or normal BMD with at least one clinical risk factor for osteoporosis. Women were randomized into five groups: bazedoxifene 10, 20 or 40 mg/day; raloxifene 60 mg/day; or placebo. The primary end point was BMD changes at

the lumbar spine; the secondary end points were BMD changes at the hip, bone turnover markers and lipid profile. The results of 1434 women in the intent-to-treat population (mean age: 58 years) revealed that bazedoxifene at all doses and raloxifene prevented bone loss at all skeletal sites. Relative to placebo, the relative percentage change in BMD with bazedoxifene 10, 20 and 40 mg and raloxifene 60 mg at the lumbar spine was 1.08 ± 0.28, 1.41 ± 0.28, 1.49 ± 0.28 and 1.49 ± 0.28%, respectively. Serum C-telopeptide, a marker of bone resorption, decreased by 25, 24 and 22%, respectively, with bazedoxifene 10, 20 and 40 mg, compared with 32% with raloxifene and 13% with placebo ($p < 0.001$ for all comparisons). Serum osteocalcin, a marker of bone formation, decreased by 21, 22 and 22% in the bazedoxifene 10, 20 and 40 mg groups, respectively, compared with 27% with raloxifene and 6% with placebo ($p < 0.001$ for all comparisons). The improved BMD and reduced bone turnover markers provided the evidence to support the efficacy of bazedoxifene for prevention of osteoporosis in postmenopausal women with normal or low BMD.

This study also demonstrated the beneficial effects on lipids. Total cholesterol and low-density lipoprotein cholesterol were significantly decreased in the bazedoxifene groups – by 4.02 and 2.94%, respectively – whereas high-density liproprotein cholesterol was increased in the 10- and 20-mg groups relative to the placebo group [22].

To evaluate the efficacy and safety of bazedoxifene for the treatment of postmenopausal osteoporosis, an international 3-year, randomized, double-blind, placebo- and active-controlled Phase III study was conducted [23,24]. Healthy postmenopausal women (n = 7492, aged 55–85 years) with osteoporosis were randomized to bazedoxifene 20 or 40 mg/day, raloxifene 60 mg/day or placebo. The primary end point was incidence of new vertebral fractures; secondary end points included nonvertebral fractures, BMD and bone turnover markers. Among the 6847 subjects included in the intent-to-treat analysis, the incidence of new vertebral fractures was significantly decreased 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 ($p < 0.05$ for all). The treatment effect was similar between subjects with and without prevalent vertebral fracture. The incidence of nonvertebral fractures with bazedoxifene or raloxifene was not significantly different to placebo. In a *post hoc* analysis of a subgroup of 1772 women at higher risk of fracture with one or more risk factors at baseline femoral neck T-score < -3.0 and/or one or more moderate-to-severe vertebral fracture or more than two mild vertebral fractures), bazedoxifene 20 mg showed a 50% reduction in nonvertebral fracture risk relative to placebo ($p = 0.02$) and 44% relative to raloxifene 60 mg ($p = 0.05$). Bazedoxifene significantly improved BMD and reduced bone marker levels ($p < 0.001$ vs placebo). Lumbar spine BMD significantly increased by 2.21 and 2.38% with bazedoxifene 20 and 40 mg, respectively, compared with 0.88% for placebo (both $p < 0.001$). The differences in total hip BMD from baseline to 3 years for bazedoxifene 20 and 40 mg were 0.27 and 0.9%, respectively, compared with -0.83% for placebo ($p < 0.001$). Compared with placebo, bazedoxifene significantly reduced serum markers of bone turnover throughout the study. At 12 months, bazedoxifene 20 and 40 mg and raloxifene 60 mg significantly reduced serum osteocalcin by 37, 39 and 41%, respectively (placebo 21%; $p < 0.001$ for all). The respective percentage reduction for serum C-telopeptide, a marker of bone resorption, was 46, 49 and 55% (placebo 27%; $p < 0.001$ for all).

Bazedoxifene significantly reduced the risk of new vertebral fracture in postmenopausal women with osteoporosis and decreased the risk of nonvertebral fracture in subjects at higher fracture risk.

In a 2-year extension study with the same end points, 4216 postmenopausal women with osteoporosis were enrolled in this 2-year extension of a 3-year Phase III trial. The raloxifene arm was discontinued after 3 years; subjects receiving bazedoxifene 40 mg were transitioned to bazedoxifene 20 mg after 4 years [25].

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. Nonvertebral 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 [≥2 mild] vertebral fracture[s]), bazedoxifene 20 mg reduced nonvertebral fracture risk versus placebo (37%; $p = 0.06$); combined data for bazedoxifene 20 and 40/20 mg reached statistical significance (34% reduction; $p < 0.05$). Bazedoxifene significantly increased BMD and reduced bone turnover versus placebo ($p < 0.05$) and was generally safe and well tolerated.

The findings after 5 years were consistent with those at 3 years and confirmed the sustained antifracture effect of bazedoxifene on new vertebral fractures in postmenopausal osteoporotic women and on nonvertebral fractures in the higher-risk subgroup of women. The current findings also suggest that factors other than changes in BMD may contribute to a reduction in fracture risk with an antiresorptive agent such as bazedoxifene, including reduction in bone turnover and potential improvement in bone material properties and/or microarchitecture [25].

Safety & tolerability

In the international Phase III 3-year core study with 7492 participants, bazedoxifene 20 and 40 mg was well tolerated and safe [23]. These findings were confirmed in the extension study at 5 years [25]. In both studies, there was no significant difference in the incidence of serious adverse events, adverse events (AEs), death rate or drop-out rate between the bazedoxifene treatment groups and placebo group. The most common AEs included back pain, arthralgia, pain, flu syndrome, infection, accidental injury, abdominal pain, headache and hypertension. Incidence of hot flushes and leg cramps in the bazedoxifene groups was higher than with placebo; most of these AEs were mild-to-moderate in severity and did not result in study discontinuation. In addition, clinical laboratory tests indicated no clinically relevant safety findings.

The incidence of cardiovascular events was low in all treatment groups, with no significant differences between the groups. The incidence of venous thromboembolic events, hot flushes and leg cramps in the bazedoxifene groups were comparatively higher than the placebo group [23–25] but were similar to the raloxifene group [23,24]. The incidence of deep vein thrombosis with bazedoxifene 20 and 40 mg was 0.3 and 0.5%, respectively, compared with 0.5% with raloxifene and 0.1% with placebo. The incidence of hot flushes with bazedoxifene 20 and 40 mg was 12.6 and 13.0%, respectively, compared with 12.0% with raloxifene and 6.3% with placebo. In the extension study the incidence of deep vein thrombosis was higher among the bazedoxifene groups (0.5 and 0.6% for bazedoxifene 20 and 40/20 mg, respectively) than the placebo group (0.2%; overall $p < 0.05$). The incidence of pulmonary embolism or retinal vein thrombosis was similar among groups.

Endometrial carcinoma and endometrial hyperplasia were similar to placebo [23]. The incidence of breast carcinoma was low in this study, at 0.3% with bazedoxifene 20 mg and 0.2% with bazedoxifene 40 mg, as compared with 0.4% for both raloxifene and placebo groups (overall p-value not significant). Breast cysts and fibrocystic breast disease were significantly lower in the bazedoxifene groups (0.7 and 0.6% for 20 and 40 mg, respectively) than raloxifene (1.7%) and placebo (1.0%). Similar results were reported in the extension study, suggesting that bazedoxifene – like other SERMs – might have a protective effect on breast cancer [25]. No significant difference was shown in the incidence of stroke between groups and there were no case reports of death due to ischemic stroke in the 3-year core study.

Conclusion

Bazedoxifene is a third-generation indole group SERM developed for use for the prevention and treatment of postmenopausal osteoporosis. The antagonistic action on breast tissue and the absence of agonistic action on the endometrium, while having agonistic activity on the skeleton, suggests that bazedoxifene could be a promising new therapy for the management of postmenopausal osteoporosis and prevention of breast cancer. Based on currently available data from clinical trials, bazedoxifene is safe and effective for both prevention and treatment of osteoporosis. In healthy postmenopausal women, bazedoxifene prevents bone loss, reduces bone turnover and maintains BMD. In postmenopausal women with osteoporosis, bazedoxifene significantly decreases the incidence of new vertebral fractures, increases BMD and reduces bone turnover. In a subgroup of postmenopausal women at higher risk of osteoporosis, bazedoxifene decreases the incidence of nonvertebral fracture. Furthermore, combinations of bazedoxifene and conjugated estrogen improve BMD and reduce hot flushes without endometrial and breast stimulation. Further studies of the long-term safety and efficacy of bazedoxifene alone and in combination with conjugated estrogen are in progress.

Expert opinion

SERMs are nonsteroidal compounds with variable clinical profiles depending on their binding properties to ERα and ERβ receptors in different target organs, in particular the uterine endometrium, breast, bone, lipoproteins, cardiovascular system and CNS. Unlike other antiosteoporosis agents that are bone selective, SERMs have extraskeletal actions that provide additional benefits to postmenopausal women. Preclinical

and clinical studies demonstrate that bazedoxifene is an effective agent for the prevention and treatment of postmenopausal osteoporosis. Phase III studies have demonstrated beneficial effects in preventing bone loss in postmenopausal women with normal or osteopenic BMD. In postmenopausal women with osteoporosis, bazedoxifene improves BMD and reduces new vertebral fracture risk. In subjects at higher risk for fracture, bazedoxifene significantly reduces the incidence of nonvertebral fracture risk in *post hoc* analysis. Safety studies have also shown that bazedoxifene is safe and well tolerated. There was no stimulation of the endometrium despite estrogen-antagonistic action on the breast and reduction in the incidence of breast cyst and fibrocystic breast disease. Although the incidence of venous thromboembolic events, hot flushes and leg cramps is higher with bazedoxifene treatment, the rates are similar to those for raloxifene, another SERM currently marketed for prevention and treatment of osteoporosis. In 2007, the FDA released an approvable letter for bazedoxifene for the prevention of postmenopausal osteoporosis. Based on data from Phase III clinical trials, bazedoxifene is also likely to receive approval for the treatment of postmenopausal osteoporosis. Further studies are needed to assess its efficacy on breast cancer prevention.

Future perspective

The last 25 years have seen the development of a plethora of new, effective agents for the treatment of osteoporosis. The efficacy of these agents in reducing fractures varies at different skeletal sites. Despite the availability of newer agents, selective estrogen-receptor modulators will continue to play a major role in fracture prevention in younger postmenopausal women, especially those at increased risk of breast cancer. The current challenge is to increase awareness of osteoporosis in early postmenopausal women to increase the treatment rate of osteopenia and osteoporosis in at-risk groups and to improve the adherence rate of treated patients. Establishment of structured osteoporosis programs and empowerment of patients into treatment programs is likely an effective approach in managing this major public health problem.

Executive summary

Aims of prevention & treatment of osteoporosis

- Prevention of bone loss in postmenopausal women without osteoporosis.
- Reduction of fractures in women with postmenopausal osteoporosis.
- Beneficial effect on bone mineral density and bone turnover markers.
- Beneficial effects on lipoprotein cholesterols.
- No stimulatory action on uterine endometrium or breast tissue.

Rationale for new treatment options

- Bazedoxifene is a new selective estrogen-receptor modulator (SERM) with both skeletal and nonskeletal actions. Its multiple actions provided additional benefits in younger postmenopausal women seeking preventive therapy against bone loss and older postmenopausal women with osteoporosis.

Bazedoxifene: a new SERM for osteoporosis

- Bazedoxifene is a third-generation indole group SERM developed for use alone or in combination with estrogen for the prevention and treatment of postmenopausal osteoporosis.
- Preclinical studies with bazedoxifene have demonstrated estrogen agonist effects on the skeleton and lipid metabolism, but not on breast and uterine endometrium.
- Phase III clinical studies have shown that bone loss in postmenopausal women without osteoporosis is prevented and vertebral fractures in women with postmenopausal osteoporosis reduced.
- In women at high risk of fracture with multiple risk factors, bazedoxifene reduces nonvertebral fracture risk.
- Clinical trials with bazedoxifene have shown beneficial effects on bone mineral density and bone turnover markers.
- In comparison with SERMs currently available in clinical practice, bazedoxifene demonstrates fewer uterine effects. There is little or no stimulation of breast and endometrium.

Bazedoxifene in clinical practice

- Bazedoxifene could be a promising new therapy for the management of postmenopausal osteoporosis.
- Bazedoxifene is safe and effective for both prevention and treatment of osteoporosis.
- In healthy postmenopausal women, bazedoxifene prevents bone loss, reduces bone turnover and maintains bone mineral density.
- In postmenopausal women with osteoporosis, bazedoxifene significantly decreases the incidence of new vertebral fractures, increases bone mineral density and reduces bone turnover.
- In women at high risk of osteoporosis, bazedoxifene decreases the incidence of nonvertebral fracture.

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▪ **WHI study addresses the efficacy and safety of long-term estrogen and progestin in postmenopausal women. The results led to the re-evaluation of the indication for long-term hormonal replacement therapy in healthy postmenopausal women and the use of hormonal replacement therapy in the treatment of osteoporosis.**

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