Bazedoxifene is a new drug which belongs to the group of modulators selective for oestrogen receptors (SORMS), a class of drugs which act selectively on oestrogen receptors (ORs). Recently approved in the European Union and in the regulatory review process in the United States for the prevention and treatment of postmenopausal osteoporosis, bazedoxifene has appeared on the market as a daily oral drug for the treatment of postmenopausal osteoporosis.

The latest clinical data on the modulators selective for oestrogen receptors has served as a base for the re-evaluation of the SORM concept. The SORMs have effects on tissues which contain ORs, such as the breast, bone, uterine and genitourinary tissue, and brain, and on markers for cardiovascular risk. The current evidence indicates that each SORM has a unique range of clinical activity. The differences in the patterns of actions of the SORMs suggest that each clinical variable should be evaluated individually, and that the conclusions around any particular SORM can only be established through appropriate clinical trials.

The action mechanism of the SORMs occurs through the bonding of two types of oestrogen receptors: alpha (OR-α) and beta (OR-β). The SORMs have agonistic and antagonistic properties at the same time, depending on the type of tissue. This is explained, in part, by the availability of different sub-types of ORs in different tissues.

Effects of bazedoxifene on different tissues of the body
Bazedoxifene has shown an affinity for the OR-α and betas (OR-β), with a slightly stronger affinity for the OR-α. They act as competitive inhibitors of estradiol in the oestrogen receptors, which indicates an antagonistic effect in the presence of high levels of estradiol, whilst it has an agonistic effect at low levels of estradiol.

Safety of the endometrium and breast is an important consideration in evaluating therapy with SORMs; the clinical development of various SORMs which have been being researched for postmenopausal osteoporosis have been suspended, in part, because of concerns about endometrial safety.

Effect on the endometrium
Endometrial hyperplasia is a surrogate marker for the development of endometrial cancer. The histological classification of endometrial hyperplasia shows transitions from simple hyperplasia (a benign lesion) through to adenomatose hyperplasia or atypical hyperplasia. While some SORMs such as tamoxifen clearly induce endometrial hyperplasia (an oestrogenic agonist effect), and increase the risk of developing endometrial cancer, others, such as raloxifene, do not appear to have an agonistic effect on the endometrium.

Preclinical data
The wet weight of the uterus of an immature rat is an accepted animal model for measuring oestrogenic effects. An increase in the wet weight of the uterus indicates a response to the oestrogen or the stimulation of the uterus. In evaluating different doses of bazedoxifene, with a dose of 0.5 mg/kg there was an increase in wet weight of the rat uterus.
weight of the uterus of 35%, while at a dose of 5 mg/kg, paradoxically, there was no significant difference in weight. It was notable that the increase in weight with the 0.5 mg/kg dose was not accompanied by hypertrophy of the luminal epithelial cells or hyperplasia, hypertrophy of the myometrium or luminal distension (Figure 1). Bazedoxifene does not stimulate the oestrogen receptors of the uterus at a dose of 0.5 mg/kg, while a dose of 5 mg/kg is antagonistic in the rat animal model.

Clinical data

The effects of bazedoxifene on the endometrium were evaluated in a total of 497 healthy postmenopausal women (average age: 53 years) in a two-part study, double blind, randomised and controlled with active treatment and placebo. All retained their uterus, and received at least one dose of medication, and a vaginal ultrasound was carried out at the start and at least once more during the follow up.

In the first part of the study, 302 women received bazedoxifene daily of 2.5, 5, 10 or 20 mg, 0.625/2.5 mg of oestrogen combined with medroxyprogesterone acetate (CEO/MPA), or a placebo, for 6 months. There were no significant differences in endometrial thickness with doses of 2.5 to 20 mg/day in comparison with the placebo, while there was a small but significant increase in endometrial thickness with CEO/MPA in comparison with the placebo (p < 0.05). Bazedoxifene at 10 and 20 mg significantly reduces the endometrium stimulated with combined equine oestrogen (COE). Due to the first results of this study being favourable, it was broadened for a second phase.

In the second phase of the study (N=497), bazedoxifene at doses of 30 and 40 mg/day is associated with a significantly lower change in endometrial thickness in comparison with the placebo (p<0.001), indicating a greater antagonism in the endometrium with the higher doses. None of the biopsies showed endometrial hyperplasia. It was concluded that bazedoxifene in doses of up to 40 mg/day is well tolerated and does not stimulate the endometrium. At doses of 2.5 to 20 mg/day the average change in the endometrial thickness from the start was no different from that observed with the placebo. The average change in thickness with 30 and 40 mg/day was significantly less in comparison with those treated with the placebo, which suggests antagonistic action on the ORs of the endometrium, a feature which had not previously been reported with any other SORM.

Bazedoxifene has been evaluated in two large Phase III prospective studies, for the prevention and treatment of osteoporosis.

In a two year study of 10 healthy postmenopausal women at risk of osteoporosis (N= 1,583; average age, 57.6 years), randomly allocated to daily treatment with bazedoxifene at 10, 20 or 40 mg, raloxifene at 60 mg, or placebo, the endometrial thickness with bazedoxifene endometrial thickness remained stable during the period of treatment of two years, without differences from the start, or compared with the placebo. There were no diagnoses of hyperplasia or endometrial cancer with the treatment with bazedoxifene, nor were there significant differences in the incidence of endometrial polyps between the placebo (3.5%) and bazedoxifene at 10, 20 or 40 mg (2.2%, 3.4% and 2.3% respectively) or with 60 mg of raloxifene (4.7%).

In the 3 year reference trial, in the population of postmenopausal osteoporotic women (N= 7,492; average age, 66.4 years) randomly allocated to bazedoxifene at 20 or 40 mg, raloxifene at...
60 mg or a placebo, who at the start of the study presented an endometrial thickness of 5 mm or less determined by transvaginal ultrasound, the long term therapy with bazedoxifene showed it to have good levels of safety in the endometrium, ovaries and breast\(^6\). The changes in endometrial thickness from the start with bazedoxifene were no different from those of the placebo. The incidence of endometrial polyps was similar between the groups on bazedoxifene and the placebo\(^6\). There was a report of endometrial hyperplasia in each treatment group, endometrial carcinoma was reported in two, two and three participants treated with 40 mg bazedoxifene, 60 mg of raloxifene and the placebo, respectively\(^6\). In general, bazedoxifene was associated with a neutral effect on the endometrium similar to that of the placebo, since the ultrasound tests did not show clinically significant changes in endometrial thickness. The incidence of endometrial hyperplasia, cancer or polyps did not increase in comparison with the placebo. A higher proportion of participants treated with raloxifene were diagnosed with endometrial polyps in comparison with those treated with bazedoxifene or the placebo in this study. The treatment with raloxifene was associated with a significant increase in endometrial thickness at 12 months in relation to the placebo (p= 0.01). A small but significant increase in endometrial thickness had already been observed in a large randomised trial in postmenopausal women treated with raloxifene, although the histological reviews in this and other studies did not show a higher risk of hyperplasia or cancer of the endometrium.

**Effects in mammary tissue**

Prospective studies have found that some SORMs reduce the risk of breast cancer by reducing the levels of endogenous estradiol\(^7\). Tamoxifen and raloxifene block the effects of endogenous oestrogens in the breast 16 and reduce the risk of breast cancer\(^7\).

- **Preclinical data**

  The stimulatory effect of an agonist on the ORs induces a proliferation in the MCF-7 cell line (human cells of mammary adenocarcinoma). Bazedoxifene does not promote the proliferation of these mammary cells, and in the presence of cells treated with 17-β-stradiol, inhibits this proliferation\(^8\). This inhibition is dependent on the dose, and there is evidence that bazedoxifene is probably an antagonist in this tissue. The effect of raloxifene in this tissue is similar\(^8\).

- **Effect on mammary pain**

  Self-referred mammary pain was evaluated in a 6 month trial in 351 postmenopausal women randomly selected to receive bazedoxifene at 2.5, 5, 10 or 20 mg, CEO+MPA or a placebo\(^7\). The women who received CEO+MAP reported a significant increase in mammary pain; in women who took any dose of bazedoxifene it was not significantly different from the placebo. Because of these results the study was extended to include 236 additional postmenopausal women to evaluate bazedoxifene at 20 mg and 40 mg compared with a placebo. It was confirmed that mammary pain was no different with 20 mg bazedoxifene than with the placebo, and that the 40 mg dose was associated with a significant reduction in mammary pain in comparison with the placebo (p= 0.034)\(^7\).

- **Mammographic density**

  An increase in mammographic density is one of the main risk factors known for breast cancer\(^8\), and a higher risk of breast cancer with a higher mammary density may reflect the cumulative effects of the oestrogens on mammary tissue.

  The effects of the SORMs on mammary density is of clinical interest, given the continuing development of these agents for use in postmenopausal women. Studies with tamoxifen and raloxifene have provided evidence that these SORMs do not affect mammographic density\(^9\).

  A retrospective review of the mammograms of a subset of women who had participated in the reference trial for the treatment of osteoporosis\(^12\) showed that treatment with bazedoxifene at 20 and 40 mg over 2 years did not affect the age-related changes in mammary density evaluated by digital mammography, and this effect was similar in those on raloxifene and the placebo\(^12\).

  The greatest reduction in mammary density normally occurs at around 45 years of age, stabilising at around 60 years of age\(^22\). Given that the women who participated in this study had an average age of approximately 59 years and were almost 13 years postmenopausal, it is reasonable to expect that the majority of these women would already have experienced a significant reduction in mammary density related to their age before they joined the study. Therefore, the effects of bazedoxifene on mammary density in recently menopausal women could be different to that of the older menopausal women who participated in this study, about which better information is needed.

- **Mammary pathology**

  As has been shown with other SORMs, in the Phase III study which compared bazedoxifene at doses of 20 or 40 mg/day, raloxifene at 60 mg/or placebo, at 3 years fewer women presented with mammary cysts and/or fibrocystic mammary disease with bazedoxifene at 20 and 40 mg compared with raloxifene, although there was a lower frequency in those groups treated with bazedoxifene than in the placebo or raloxifene groups\(^13\).

  In another study of similar design to study the safety of bazedoxifene in the endometrium, ovary and breast\(^13\), there was a significantly lower incidence of fibrocystic mammary disease with bazedoxifene compared with 60 mg of raloxifene, although the
Table 1. Adverse events associated with different doses of bazedoxifene compared with a placebo

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>BZD 10 mg (n = 321)</th>
<th>BZD 20 mg (n = 322)</th>
<th>BZD 40 mg (n = 3,191)</th>
<th>RLX 60 mg (n = 311)</th>
<th>Placebo (n = 310)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>306 (95.3)</td>
<td>309 (96.0)</td>
<td>301 (94.4)</td>
<td>287 (92.3)</td>
<td>297 (95.8)</td>
</tr>
<tr>
<td>Any adverse event arising from treatment</td>
<td>299 (93.1)</td>
<td>304 (94.4)</td>
<td>292 (91.5)</td>
<td>279 (89.7)</td>
<td>289 (93.2)</td>
</tr>
<tr>
<td>Deaths</td>
<td>2 (0.6)</td>
<td>0 (0.0)</td>
<td>3 (0.9)</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Any adverse event which results in abandonment</td>
<td>54 (16.8)</td>
<td>55 (17.1)</td>
<td>58 (18.2)</td>
<td>43 (13.8)</td>
<td>48 (15.5)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>29 (9.0)</td>
<td>37 (11.5)</td>
<td>33 (10.3)</td>
<td>29 (9.3)</td>
<td>28 (9.0)</td>
</tr>
</tbody>
</table>

Adverse effects of special interest

- **Myocardial infarction**
  - BZD 10 mg: 0
  - BZD 20 mg: 2 (0.6)
  - BZD 40 mg: 1 (0.3)
  - RLX 60 mg: 0
  - Placebo: 1 (0.3)

- **Cerebral haemorrhage**
  - BZD 10 mg: 1 (0.3)
  - BZD 20 mg: 0
  - BZD 40 mg: 0
  - RLX 60 mg: 0
  - Placebo: 0

- **Cerebral ischemia**
  - BZD 10 mg: 0
  - BZD 20 mg: 0
  - BZD 40 mg: 0
  - RLX 60 mg: 0
  - Placebo: 1 (0.3)

- **Cerebrovascular accident**
  - BZD 10 mg: 0
  - BZD 20 mg: 0
  - BZD 40 mg: 1 (0.3)
  - RLX 60 mg: 0
  - Placebo: 0

- **Deep vein thrombosis**
  - BZD 10 mg: 0
  - BZD 20 mg: 2 (0.6)
  - BZD 40 mg: 0
  - RLX 60 mg: 0
  - Placebo: 1 (0.3)

- **Phlebitis (superficial)**
  - BZD 10 mg: 1 (0.3)
  - BZD 20 mg: 1 (0.3)
  - BZD 40 mg: 3 (0.9)
  - RLX 60 mg: 0
  - Placebo: 1 (0.3)

- **Pulmonary embolism**
  - BZD 10 mg: 0
  - BZD 20 mg: 0
  - BZD 40 mg: 1 (0.3)
  - RLX 60 mg: 0
  - Placebo: 0

- **Retinal thrombosis**
  - BZD 10 mg: 0
  - BZD 20 mg: 0
  - BZD 40 mg: 0
  - RLX 60 mg: 1 (0.3)
  - Placebo: 0

- **Breathlessness**
  - BZD 10 mg: 63 (19.6)
  - BZD 20 mg: 67 (20.8)
  - BZD 40 mg: 77 (24.1)
  - RLX 60 mg: 58 (18.6)
  - Placebo: 44 (14.2)

- **Cramp**
  - BZD 10 mg: 30 (9.3)
  - BZD 20 mg: 39 (12.1)
  - BZD 40 mg: 38 (11.9)
  - RLX 60 mg: 37 (11.9)
  - Placebo: 36 (11.6)


number of women and of mammary events was too small to allow definitive conclusions to be drawn. In general, the incidence of adverse events related to the breast in groups treated with bazedoxifene was similar to that reported in the placebo group. There were fewer cases of breast cancer with bazedoxifene in comparison with the placebo or raloxifene13. These findings suggest a possible protector effect of bazedoxifene on the breast. However, we do not have data available to calculate with precision the reduction in the risk of breast cancer attributable to bazedoxifene, or to estimate the number of women who need to be treated to prevent a single case of invasive breast cancer.
Effects in other tissues
Bazedoxifene has been shown to be well tolerated in the population of healthy postmenopausal women at risk of osteoporosis-related fractures. The incidence of adverse events, serious adverse events and abandonment of treatment due to adverse events were similar across all the treatment groups.

- No statistically significant differences were observed between the treatment groups for cardiovascular events.
- In the two Phase III studies, bazedoxifene showed favourable effects on the lipid metabolism in postmenopausal women, with a reduction in total cholesterol and LDL-cholesterol, an increase in HDL-cholesterol and neutral effects on the triglycerides. However, it is still to be determined if the changes observed in the lipid profile with the treatment with bazedoxifene have some clinical relevance.
- No adverse effects have been shown on the ovary in any of the clinical trials which evaluated the effects of bazedoxifene at 10, 20 or 40 mg, on ovarian volume, number or size of ovarian cysts or on the incidence of ovarian cancer over 24 months.
- There is no evidence of other adverse gynaecological effects, including neoplasias in the uterine neck, growth of uterine fibroids, uterine haemorrhage and vaginal bleeding.

Adverse effects
As a SORM, it would be expected that bazedoxifene would have the “classic” adverse effects, including those related to hypoestrogenism (shortness of breath, mood swings and vaginal dryness); and, on the other hand, agonistic oestrogenic effects (a higher risk of thromboembolisms and thrombophlebitis, nausea, dyspepsia, peripheral oedema, migraine and arthralgia).

- Although the preclinical data suggested that bazedoxifene could not have vasomotor effects in postmenopausal women, the incidence of breathlessness and leg cramps in the Phase III trial was significantly higher in the bazedoxifene and raloxifene groups than in the placebo group (p<0.05). However, the majority of the episodes of breathlessness were light to moderate and did not continue on discontinuation of the treatment.
- In the 2 year prevention study the incidence of deep vein thrombosis was low and similar among all groups (0% with bazedoxifene at 10 mg and 40 mg and raloxifene at 60 mg, 0.6% in bazedoxifene at 20 mg and 0.3% with the placebo). In the 3 year treatment study the incidence of all the venous thromboembolic events (pulmonary embolism, deep vein thrombosis and retinal vein thrombosis) was higher in the active treatment groups (raloxifene or bazedoxifene) compared with the placebo, although the incidence was generally very low (<1%) and was not statistically significant. Similar findings were observed in the extension study of 2 years.

Adjustment of dosage with age
There are currently no data available on the use of bazedoxifene in premenopausal women. This group may need protection against osteoporosis in situations such as hypogonadism and premature ovarian insufficiency. Bazedoxifene has been studied in women during the first years of the menopause. There no data on its use in senility. However, it is not expected that the use of bazedoxifene in patients of advanced age requires an adjustment in dosage since, differently from other drugs, the way bazedoxifene is metabolised does not appear to be affected by age.

Future perspectives
A new approach to therapy or the menopause is tissue selective oestrogen complex (TSEC), which associates a SORM with one or more oestrogens, this combination having the objective of achieving an optimum balance of agonist/antagonist activity on the oestrogen receptor for the treatment of menopausal symptoms and the prevention of loss of bone mass. The first TSEC in clinical development associates bazedoxifene with combined oestrogens (CEO). Phase III clinical trials of 20 mg and 40 mg of bazedoxifene, each with a CEE of 0.45 or 0.625 mg, have shown a significant increase in bone mineral density (BMD) and an improvement in vasomotor symptoms and vulvo-vaginal atrophy, and at the same time guaranteeing endometrial safety in postmenopausal women.

Conclusion
The available data on bazedoxifene reflect a favourable safety profile with respect to the endometrium, ovary and breast in healthy women in recent menopause at risk of osteoporosis. It is important to highlight the fact that the safety data at 5 years are, in general, similar to those at 3 years, based on the findings of a recent two year extension study.

The use of bazedoxifene to reduce the risk of fracture may contribute to the reduction in the risk of breast cancer, without risk to the uterus or ovaries. The most significant difference between bazedoxifene and raloxifene appears to be the inhibitory effect of the former on the endometrium, which allows the association of bazedoxifene with CEO. The combination of bazedoxifene and CEO has shown an improvement in BMD and in vasomotor symptoms without stimulatory effects on the endometrium or breast. The use of bazedoxifene to replace gestagen as a protector of the endometrium in hormonal therapy is a potential future application of bazedoxifene.

New clinical trials should clarify the differences between bazedoxifene and other SORMs and clinical experience will help us to define the clinical value of bazedoxifene in the treatment of osteoporosis.
Conflict of interests
Dr. R Sánchez-Borrego declares his membership of the Advisory Board on Bazedoxifene of the Pfizer Laboratories, Spain. Dr. F. Lugo declares that he has no conflicts of interest.
No person with a working relationship with the Company has been involved in the preparation of this article.

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