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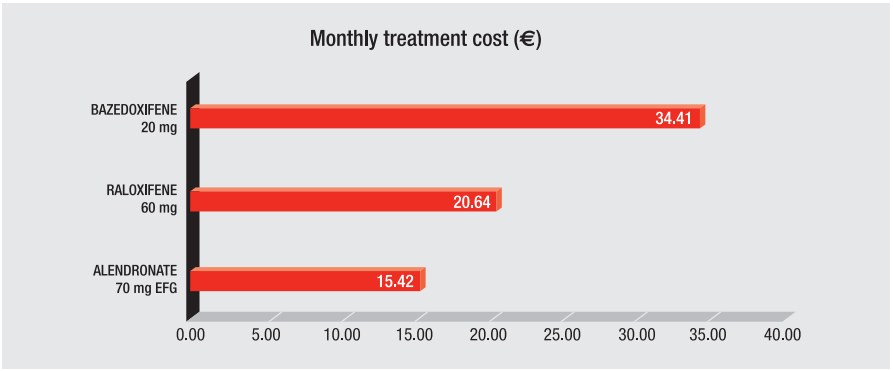
Bazedoxifene▲ (Conbriza®) and osteoporosis

For every 5 radiological vertebral fractures avoided there is one case of thromboembolism

Presents a very questionable risk-benefit relationship



Therapeutic indications[1]

Bazedoxifene is indicated for the treatment of postmenopausal osteoporosis in women at increased risk of fracture. A significant reduction in the incidence of vertebral fractures has been demonstrated; efficacy on hip fractures has not been established.

Mechanism of action and pharmacodynamics[1]

Bazedoxifene belongs to a class of selective estrogen receptor modulators (SEM). It reduces bone resorption and increases bone mineral density (BMD). It acts as a estrogen-receptor antagonist in uterine and breast tissue. It is rapidly absorbed, with a tmax = 2 h and a bioavailability of 6%. It can be taken with or without food. It is metabolized mainly by glucuronidation with hardly any intervention from P450 cytochrome. The elimination half-life is approximately 30 h. The main elimination pathway is faeces (less than 1% is eliminated in urine).

Posology and form of administration[1]

The recommended dose of bazedoxifene is one 20 mg tablet once daily, at any moment of the day with or without meals. Supplements of calcium and/or vitamin D should be added to the diet, if daily intake is not sufficient.

Clinical efficacy[1,2]

In the EMA´s report there is a reference to two clinical studies regarding the effects of bazedoxifene in women with osteoporosis[2]. One of these trials is a dose finding study that includes an active branch of raloxifene, but the study only evaluated the effects on bone density[3].

The other study compared the efficacy of bazedoxifene to placebo and raloxifene with regard to the incidence of vertebral fractures diagnosed by radiological morphometric methods[4]. In this study 7,492 postmenopause women were recruited (mean age = 66 ± 6.7 years). They included women with either no previous history of fracture and with lumbar vertebral BMD beween -2.5 and -4.0 SD, or women with

- Bazedoxifene is indicated in postmenopausal osteoporosis in women at increased risk of fracture.
- It is not effective in the reduction of clinical fractures, hip or non-vertebral fractures, and has only shown a significant reduction in the incidence of morphometric-diagnosed vertebral fractures.
- The increase in the incidence of thromboembolism is similar to that observed with raloxifene. The EMA has established a risk management plan to study some alarm signals detected.
- Its price is considerably higher than raloxifene.

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.

previous fractures and lumbar vertebral BMD not worse than -4.0 SD. Follow-up was three years. Those women with vasomotor symptoms, history of thromboembolism, hypercholesterolemia or hypertriglyceridemia were excluded. The participating women received either bazedoxifene (20 or 40 mg daily), raloxifene (60 mg daily) or placebo. All women received daily treatment of 1,200 mg calcium and 400-800UI vitamin D. Among secondary variables under evaluation, it is worth mentioning the incidence of non-vertebral fractures and clinical vertebral fractures.

The incidence of radiological morphometric vertebral fractures was 2.3%, 2.5%, 2.3% and 4.1% for bazedoxifene 20 mg, bazedoxifene 40 mg, raloxifene 60 mg and placebo respectively. Both bazedoxifene and raloxifene showed significant differences compared to placebo. The risk reduction in absolute terms was 1.7% after the three year follow-up period. There were no differences between the 20 mg and 40 mg dose of bazedoxifene. Nor were there statistically significant differences between bazedoxifene and raloxifene. No significant differences were found with regard to either clinical vertebral fractures (secondary endpoints) or non-vertebral fractures.

Safety[1,2]

Adverse reactions[1]

The most frequent side effects (≥10%) were: hot flashes and muscular spasms (including paresthesia in lower limbs). Other severe though less common side effects (0.1%-1%) were: deep vein thrombosis, (0.4%) superficial thrombophlebitis, pulmonary embolism (0.3%). Less frequent (0.01-0.1%) undesirable effects included some documented cases of retinal vein thrombosis.

Contraindications[1]

Hypersensitivity to the main substance or any of its excipients (contains lactose). Presence or history of thromboembolic events. Women in child bearing age. Uterine bleeding of unexplained cause. Patients with symptoms or signs of endometrial cancer.

Special precautions for use[1]

The use of bazedoxifene is not recommended in women at increased risk of venous thromboembolism: advanced age, obesity, immobilisation, surgery, major trauma or malignancy.

It should be suspended before and during prolonged immobilisation (for example, post surgical recovery, prolonged bed rest) and resumed only after the patient is completly ambulatory. Moreover during prolonged journeys, women should be advised to move about once in a while.

Any uterine bleeding during treatment with baxedoxifene is unexpected and should be investigated thoroughly.

Use in special situations[1]

Pregnancy or lactation: should not be used. **Renal impairment:** there is no data on severe patients. No dose adjustments are required in patients with mild or moderate renal impairment. **Liver impairment:** not recommended. **Children:** not indicated. **Elderly:** no dose adjustments are necessary based on the age of patients.

Interactions[1]

In vitro studies suggest that it is improbable that bazedoxifene interacts with other medicinal products administered concomitantly via CYP mediated metabolism.

Risk Management plan of the European Medicines Agency (EMA)

The EMA proposed a study plan after authorization to evaluate the following risk potential of bazedoxifene: venous thromboembolism, ischemic stroke, atrial fibrillation, renal adenoma and carcinoma, worsening, impairment or kidney failure, cholecystitis, hypertriglyceridemia, cardiac thromboembolism and ischemia, and its use in elderly patients (these last two, given the limited information available at present).

Place in therapeutics

Pharmacological management of osteoporosis has been shown to be effective in reducing the loss of bone mass. However this improvement in BMD with respect to placebo does not necessarily mean a reduction in the risk of clinically relevant fractures in the majority of cases. Calcitonin based agents were used for many years, and no real efficacy was demonstrated in the reduction of fractures. Hormone replacement therapy was discontinued due to the excess cardiovascular risk associated with its use, in turn not justified by the benefits with regard to bone metabolism. Raloxifene, strontium ranelate, teriparatide and parathyroid hormone have not demonstrated efficacy in the prevention of hip fractures and the efficacy of biphosphonates is uncertain. The efficacy of all these drugs with regard to the prevention of vertebral fractures is of uncertain clinical relevance because the evidence was shown mainly through studies where fractures were diagnosed by morphopmetric methods (determined with uncertain diagnostic precision).

Bazedoxifene is similar to raloxifene (which has shown only limited efficacy). It is not better than placebo in the reduction of both clinical vertebral and non-vertebral fractures. Bazedoxifene has only demonstrated a reduction in radiologically diagnosed vertebral fractures using morphometric methods. This reduction was very scarce in absolute terms (1.7% after 3 years). It is difficult to know the clinical transcendence of this finding. Theoretically 59 women would be needed to treat with bazedoxifene for three years in order to avoid a morphometrically diagnosed vertebral fracture. On the other hand, there is one thromboembolic event, one case of vasodilation (hot flushes, night sweats or a hot sensation in the face) and one case of fibrocystic breast for every 333 women treated for three years. Moreover, for every 5-6 vertebral fractures diagnosed radiologically through morphometry, one case of deep vein thrombosis occurs.

Bazedoxifene´s safety profile is basically similar to that of raloxifene (although the latter has been comercialized for a longer period, and thus more safety data are available). The EMA has established a risk management plan for bazedoxifene with the aim of obtaining more information regarding the safety alarm signals detected in clinical studies.

Today the use of drugs for the reduction of the incidence of fractures is under question. The most adequate approach is the prevention of osteoporosis through hygienic and dietary measures and the prevention of falls, especially in the elderly[8].

Presentations

CONBRIZA® (Pfizer) 20 mg 28 tablets (34.41 €). Prescription medicine only.

References

A complete report on bazedoxifene can be found at: http://www.dtb.navarra.es

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