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CONJUGATED OESTROGENS BAZEDOXIFENE

DUAVIVE® FOR SYMPTOMS OF MENOPAUSE

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DRUG ASSESSMENT REPORT
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Finding it a place in therapeutics causes hot flashes

Indications

Oestrogen deficiency symptoms in postmenopausal women with a uterus for whom treatment with progestin-containing therapy is not appropriate. The experience treating women older than 65 years is limited.

Mechanism of action

Combination of conjugated oestrogens and bazedoxifene (a selective oestrogen receptor modulator (SERM)). Therapeutic group: G03CC-Estrogens, combinations with other drugs. The code of the active substance is G03CC07- Conjugated oestrogens/bazedoxifene.

Conjugated oestrogens replace the oestrogen hormones that are no longer produced in menopausal women, thereby alleviating the associated vasomotor symptoms. In turn, they cause endometrial growth, thus increasing the risk for endometrial hyperplasia and cancer. Its combination with bazedoxifene –an antagonis of uterine oestrogen receptors– reduce the risk for endometrial hyperplasia associated with the use of oestrogens in non-hysterectomised women.

Posology and Method of Administration

The recommended dose is a tablet (0.45 mg / 20 mg) once daily. Both, initiation and continuation treatment for postmenopausal symptoms should be for the shortest duration possible.

Clinical efficacy

No phase III comparative studies of oestrogens + bazedoxifene vs. oestrogens + progestin (which is the treatment of choice for menopause symptoms) have been conducted. The only trial in which the primary endpoint was the reduction in the number of hot flashes (SMART2) was placebo-controlled, with a duration of 12 weeks. Reportedly, a significant reduction was achieved in the mean number of moderate and severe hot flashes (-7.63 for oestrogens/bazedoxifene vs. -4.92 for placebo; with a baseline number of daily hot flashes of 10 hot flashes/day), and a fall in the daily severity score of hot flashes (-0.87 vs. -0.26 respectively, with a baseline severity score of 2.3 for a maximum of 3). The effectiveness of the oestrogen/bazedoxifene combination in the treatment of vaginal atrophy has not been compared with that of the treatment of choice i.e. low-dose topical oestrogens. Its efficacy for vulvovaginal atrophy was assessed based on four combined outcomes. According to the SMART3 trial, the patients treated with oestrogens/bazedoxifene showed a significant fall in the percentage of superficial vaginal cells and the number of parabasal cells at week 12. However, no statistically significant differences were observed in the reduction of vaginal pH or the improvement of the most bothering symptoms. Therefore, the results obtained are not considered clinically relevant.

Safety

Adverse Reactions

The adverse event most frequently reported was abdominal pain, which affected more than 10% of participants. Other adverse events include vulvovaginal candidiasis, constipation, diarrhea, nausea, muscle spasms, increased blood triglycerides, arthralgia, myalgia, back pain, limb pain, nasopharyngitis, and flu.

Cases of endometrial hyperplasia were reported in two trials (SMART 1 and 5) assessing the endometrial safety of the combination. The SMART 1 trial did not meet best practice standards due to an inappropriate use of data from endometrial biopsies. In the SMART 5 trial, 12 outcomes related to endometrial safety were uncertain due to the absence of transvaginal biopsies and/or ultrasound scans. Despite these deficiencies, the drug was approved by the EMA. As long-term endometrial safety was unknown, it was included in the risk management plan.

Both, conjugated oestrogens and bazedoxifene cause thromboembolic events. Clinical trials have not shown an increased risk of thromboembolic and cardiovascular events vs. placebo. However, the duration of trials was limited (maximum: 2 years) and only 850 women received the approved dose. As a result, cardiovascular and thromboembolic safety have been included in the EMA's risk management plan.

Safety in special populations: data for women older than 65 years are limited. The use of oestrogens/bazedoxifene in patients older than 75 years with liver or renal failure or premature menopause has not been studied yet.

Three members of the EMA (Germany, France and Czech Republic) recommended against the approval of this combination, as its risk/benefit balance was negative. The reason is that its endometrial safety has not been assessed appropriately, long-term data are not available, and

RESUMEN

The oestrogen/bazedoxifene combination is indicated for the treatment of oestrogen deficiency symptoms in postmenopausal women with an intact uterus and progestin intolerance.

It has not been compared with the oestrogen/progestin combination. Approval was based on a series of pivotal placebo-controlled trials where the daily number of moderate and severe hot flashes was reduced by near 3.

Its long-term safety profile is unknown due to the short duration of trials. Endometrial, thromboembolic, and cardiovascular safety were included in the risk management plan. The adverse event most frequently reported was abdominal pain (10%).

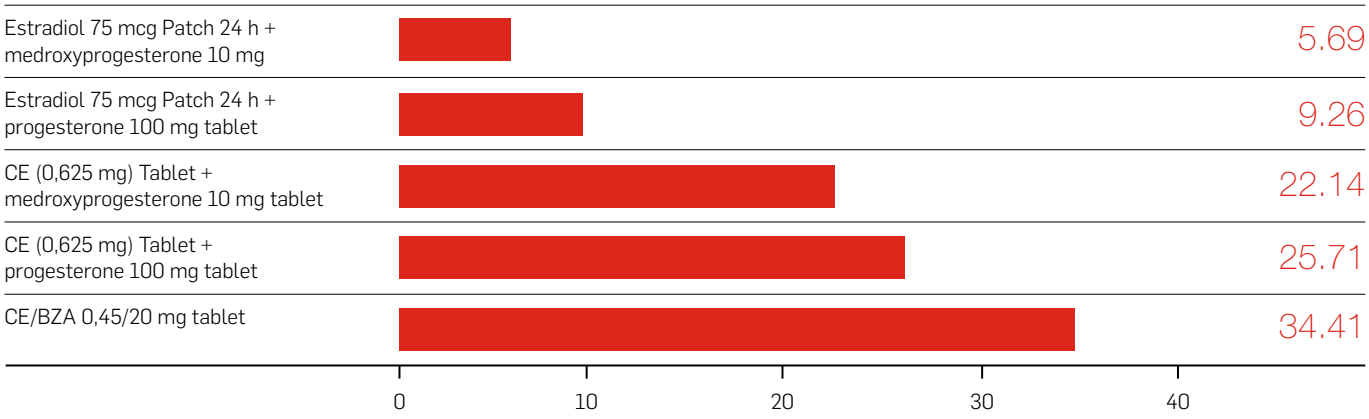
CLASSIFICATION

4	IMPORTANT THERAPEUTIC INNOVATION
3	MODEST THERAPEUTIC INNOVATION
2	SOME ADDED VALUE IN SPECIFIC SITUATIONS
1	**NO THERAPEUTIC INNOVATION**
0	INSUFFICIENT EVIDENCE

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.

28-DAY TREATMENT COST (€) / 28 DÍAS

(CE) Conjugated oestrogens. (BZA) Bazedoxifene.



data for the subgroup of patients with intolerance to progestin have not been provided.

Contraindications

Its use is CONTRAINDICATED in women with a history of breast cancer and other oestrogen-associated malignancies (endometrial cancer), undiagnosed genital bleeding, untreated endometrial hyperplasia, liver dysfunction, or hypersensitivity to the active substances or excipients of the drugs, as well as in women of childbearing age and porphyria.

Special warnings and precautions for use

Treatment should be initiated only if menopausal symptoms negatively affect the quality of life of patients. The risks and benefits of the therapy should be assessed at least once a year in all patients. Therapy should only be continued if the benefits outweigh the risks.
Women receiving this combination should not use progestin or SERMs.
No data are available on its use in patients with premature menopause.

Usage in special situations

Renal failure: Not recommended for patients with renal failure, as its pharmacokinetics have not been assessed in this type of patients yet.
Severe hepatic impairment: Contraindicated for patients with liver failure, as its safety and effectiveness have not been assessed in this type of patients.
Advanced age: No studies in women older than 75 years have been performed yet. Experience in women younger than 65 years is limited. According to the data available, dose adjustment by age is not necessary.

Interactions

Conjugated oestrogens

The metabolism of oestrogens may be increased by concomitant use of substances known to induce drug-metabolizing enzymes such as anticonvulsants, anti-infectives or herbal preparations containing St John's wort (Hypericum perforatum).
In clinical terms, an increased metabolism of oestrogens may lead to decreased effect and changes in the uterine bleeding profile.

Bazedoxifene

Concomitant use of drug-metabolising enzymes such as rifampicin, phenobarbital, carbamazepine and phenytoin may lead to decreased systemic concentrations of bazedoxifene. A reduced exposure to bazedoxifene may be associated with an increased risk of endometrial hyperplasia. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include an endometrial biopsy to exclude endometrial malignancy.
Ritonavir and nelfinavir, although known as strong inhibitors, they exhibit inducing properties when used concomitantly with steroid hormones.

Place in therapeutics

Oestrogens/bazedoxifene is a new combination for the treatment of the symptoms of menopause. Individualized therapy should be based on the intensity of symptoms, the age of the patient, cardiovascular and thromboembolic risk, and risk for breast and endometrial cancer. The combined use of progestin should be considered based on the presence or not of an intact uterus (hysterecomised vs. non-hysterectomised women).
The benefit of hormone replacement therapy outweighed the risks in women younger than 60 years of age who had been through the menopause for less than 10 years.
It is a therapeutic option for vasomotor symptoms only in non-hysterectomised postmenopausal women for whom the use of oestrogens/progestin is not appropriate or who are intolerant to progestin.
The only advantage over progestin-containing therapies is amenorrhea. Its main drawback is that long-term safety in terms of endometrial cancer is unknown.
The treatment of choice for vulvovaginal atrophy is low-dose topical drug therapy.
The combination evaluated did not show to be effective in the treatment of clinically relevant symptoms. It is not recommended for this indication.
Additionally, this combination is 25% more expensive than oestrogen/progestin therapies.
Therefore, oestrogens/bazedoxifene does not represent any significant advance. Based on its unknown long-term safety profile, its use should be limited to the treatment of moderate to intense vasomotor symptoms in postmenopausal women younger than 65 years with a uterus who are intolerant to progestin-containing therapies.

Presentations

Duavive® (0.45 mg/20 mg) 28 tablets (€34.41)

References

Based on the Evaluation report. Available at: https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/home.htm