NEW DRUGS

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Conjugated oestrogens/bazedoxifene

Approved indication: menopause
Duavive (Pfizer)
0.45 mg/20 mg modified-release tablet
Australian Medicines Handbook section 17.2.1

This product is indicated for moderate to severe vasomotor symptoms associated with menopause in women with an intact uterus. It combines conjugated equine oestrogens with bazedoxifene, a selective oestrogen receptor modulator. Bazedoxifene has been added to inhibit the stimulating effects of oestrogens on the endometrium and reduce the risk of endometrial cancer.

A placebo-controlled trial assessed two fixed-dose combinations of conjugated oestrogens/bazedoxifene (0.45 mg/20 mg, 0.625 mg/20 mg) in women who were having at least seven moderate to severe hot flushes a day. They were aged 42–63 years with an average of 4.5 years since menopause. After 12 weeks of treatment, both doses significantly reduced the number and severity of hot flushes (see Table).[1]

In a safety cohort of 3168 women, abdominal pain was the most frequently reported adverse event (≥10%). Other common events included muscle spasms (8%), myalgia (7.9%), nausea (6.6%), diarrhoea (5.9%) and constipation (4.7%). Increases in triglycerides were quite common (1.8% of women) so annual blood monitoring should be considered.

In longer term trials (12–24 months), the 0.45 mg/20 mg dose did not appear to significantly increase bleeding events (including uterine bleeding)[2] and breast density or breast pain[3] compared to placebo. The incidence of endometrial hyperplasia was low with the 0.45 mg/20 mg dose (1/335 women) and was similar to the incidence in the placebo group (1/354 women). An increase in endometrial thickness was significantly more common with conjugated oestrogens/bazedoxifene than with placebo.[4]

Cases of pulmonary embolism, deep vein thrombosis, retinal vein thrombosis and thrombophlebitis have been reported with this drug but were rare (<1/1000). In common with other oestrogen-containing drugs, women who have had venous thromboembolism, a thrombophilic disorder, myocardial infarction or ischaemic stroke should not be prescribed this product. Other contraindications include genital bleeding, endometrial hyperplasia, a history of breast cancer or oestrogen-dependent tumours, liver disease and porphyria. The combination is not recommended in women with renal impairment.

The recommended dose is one tablet a day taken continuously. Following oral administration, maximum serum concentrations of the conjugated oestrogens are reached after 8.5 hours and maximum concentrations of bazedoxifene are reached after 2 hours. Their half-lives are 17 and 30 hours respectively. The oestrogens are eliminated in urine and most of the bazedoxifene dose is eliminated in the faeces.

Oestrogens are partially metabolised by cytochrome P450 (CYP) 3A4 so co-administration of inducers of this enzyme could potentially reduce serum concentrations of the oestrogens. Co-administration with a CYP 3A4 inhibitor had minimal impact on the drug's pharmacokinetics. Bazedoxifene is metabolised by uridine diphosphate glucuronosyltransferase therefore concomitant drugs that induce this enzyme (e.g. rifampicin, phenytoin) may reduce bazedoxifene concentrations and increase the risk of endometrial hyperplasia. Drugs such as ibuprofen, atorvastatin and azithromycin do not appear to interact with bazedoxifene.

This oestrogen/bazedoxifene combination is effective for reducing vasomotor symptoms in postmenopausal women compared to placebo. However, it is

Table **Efficacy of conjugated oestrogens/bazedoxifene for vasomotor symptoms associated with menopause**

Oestrogens/bazedoxifene daily dose or placebo (randomised women)	Mean number of moderate–severe hot flushes/day		Mean severity score of hot flushes/day *	
	baseline	12 weeks	baseline	12 weeks
0.45 mg/20 mg (133)	10.3	2.8	2.3	1.4
0.625 mg/20 mg (133)	10.4	2.4	2.3	-
placebo (66)	10.5	5.4	2.3	2

* severity score for mild hot flush = 1, moderate hot flush = 2, severe hot flush = 3
Source: Reference 1

unclear how its efficacy will compare to oestrogen/progestogen combinations. The European Medicines Agency concluded that this product should be reserved for women who cannot take oestrogen/progestogen combinations. Data on the use of this drug for longer than two years are limited. It should be used for the shortest duration possible with regular patient monitoring.

T T manufacturer provided additional useful information

REFERENCES

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the European Medicines Agency.