

# AUSTRALIAN PRODUCT INFORMATION – DUAVIVE® 0.45/20 (conjugated estrogens/bazedoxifene)

## Warning

The risk associated with DUAVIVE is unknown due to the lack of long term safety data (see Sections 4.3 Contraindications, 4.4 Special warnings and precautions for use and 4.8 Adverse effects (undesirable effects), Description of Selected Adverse Reactions).

The Women’s Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women aged 50 to 79 years (mean age 63.6 years) during 7.1 years of treatment with conjugated estrogens (0.625 mg/day) alone therapy relative to placebo. Estrogen-alone therapy is also associated with an increased risk of ovarian cancer.

## 1. NAME OF THE MEDICINE

Conjugated estrogens/bazedoxifene.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each DUAVIVE 0.45/20 modified release tablet contains 0.45 mg of conjugated estrogens (CE) and bazedoxifene acetate equivalent to 20 mg of bazedoxifene.

### Excipient(s) with known effect

Each tablet contains 96.9 mg sucrose (includes 0.7 mg sucrose as sucrose palmitate), 59.8 mg lactose monohydrate and 0.2 mg maltitol solution (a component of Opaglos 2 Clear) (see Section 4.4 Special warnings and precautions for use, Other conditions).

For the full list of excipients, see Section 6.1 List of excipients.

## 3. PHARMACEUTICAL FORM

Modified release tablet.

DUAVIVE 0.45 mg/20 mg is a pink, oval shaped, tablet marked on one side with “0.45/20”.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indication

DUAVIVE is indicated for treatment of moderate to severe vasomotor symptoms associated with menopause in women with a uterus.

- DUAVIVE should be used for the shortest duration consistent with treatment goals and risks for the individual woman.

- Experience in women older than 65 years is limited.

## 4.2 Dose and method of administration

### Dosage

The recommended dose is as a single tablet, once daily.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see Section 4.4 Special warnings and precautions for use) should be used.

Women taking DUAVIVE should not take additional progestogens, estrogens or selective estrogen receptor modulators (SERMS) (see Section 4.4 Special warnings and precautions for use).

### Method of administration

Orally.

DUAVIVE may be given at any time of day, with or without food. Tablets should be swallowed whole. Tablets should not be chewed, crushed or broken.

### Dosage adjustment

#### *Renal impairment*

The pharmacokinetics of CE/bazedoxifene have not been evaluated in patients with renal impairment. Use in this population is therefore not recommended (see Sections 4.4 Special warnings and precautions for use, Use in Renal Impairment and 5.2 Pharmacokinetic properties, Renal impairment).

#### *Hepatic impairment*

The safety and efficacy of CE/bazedoxifene have not been evaluated in patients with hepatic impairment. Use in this population is contraindicated (see Sections 4.3 Contraindications and 5.2 Pharmacokinetic properties, Hepatic impairment).

#### *Elderly*

The experience treating women older than 65 years is limited.

In 224 women included in clinical trials, aged between 65 and 75 years, no dosage adjustment was required (see Section 5.2 Pharmacokinetic properties, Elderly). DUAVIVE has not been studied in women over 75 years of age.

#### *Paediatric use*

There is no relevant use of DUAVIVE in the paediatric population (see Section 4.4 Special warnings and precautions for use, Paediatrics use).

## 4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in Section 6.1 List of excipients.

Known, suspected, or past history of breast cancer.

Known, past or suspected estrogen-dependent malignant tumours (e.g., endometrial cancer).

Undiagnosed genital bleeding.

Untreated endometrial hyperplasia.

Active or past history of venous thromboembolism (e.g., deep venous thrombosis, pulmonary embolism, and retinal vein thrombosis).

Known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency, see Section 4.4 Special warnings and precautions for use).

Active or past history of arterial thromboembolic disease (e.g., myocardial infarction, stroke).

Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal.

Pregnancy, women who may become pregnant, and nursing mothers (see Section 4.6 Fertility, pregnancy and lactation, Use in Pregnancy and Use in Lactation).

Porphyria.

#### **4.4 Special warnings and precautions for use**

For the treatment of postmenopausal symptoms, DUAVIVE should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually, and treatment should only be continued as long as the benefit outweighs the risk.

Women taking DUAVIVE should not be taking progestogens, additional estrogens or SERMs (see Section 4.2 Dose and method of administration).

DUAVIVE has not been studied in the treatment of premature menopause.

#### **Medical examination/follow-up**

Before initiating or reinstating treatment with DUAVIVE, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see Breast Cancer later in this section). Investigations, including appropriate imaging tools, e.g., mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

#### **Conditions which need supervision**

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with DUAVIVE, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see Venous thromboembolism below)
- Risk factors for estrogen-dependent tumours, e.g., 1st degree heredity for breast cancer
- Hypertension
- Liver disorders e.g., hepatic adenoma, hepatic haemangiomas
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or severe headache
- Systemic lupus erythematosus
- A history of endometrial hyperplasia (see Endometrial hyperplasia and carcinoma below)
- Epilepsy
- Asthma
- Otosclerosis.

### **Reasons for immediate withdrawal of therapy**

Therapy should be discontinued where a contradiction to therapy presents, e.g.,

- Venous thromboembolism
- Stroke
- Pregnancy
- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache.

### **Endometrial hyperplasia and carcinoma**

In women with an intact uterus, the risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among estrogen-only users varies from 2- to 12-fold greater compared with non-users, depending on duration of treatment and estrogen dose. After stopping treatment, risk may remain elevated for at least 10 years. Women taking DUAVIVE should not take additional estrogens as this may increase the risk of endometrial hyperplasia and endometrial carcinoma.

The addition of bazedoxifene in DUAVIVE reduces the risk of endometrial hyperplasia, which may be a precursor of endometrial carcinoma (see Sections 4.8 Adverse effects (undesirable effects), Description of selected adverse reactions, Endometrial cancer risks and 5.1 Pharmacodynamic properties, Clinical trials, Effects on the endometrium).

Break-through bleeding and spotting may occur during treatment. 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 endometrial biopsy to exclude endometrial malignancy.

### **Breast cancer**

The effect of DUAVIVE on the risk of breast cancer is unknown.

The overall evidence suggests a possible increased risk of breast cancer in women taking estrogen-only therapy that is dependent on the duration of therapy and age at initiation of therapy.

The Women's Health Initiative (WHI) trial found no increase in the risk of breast cancer in hysterectomised women using estrogen-only therapy (see Section 4.8 Adverse effects (undesirable effects), Description of selected adverse reactions, Breast cancer risk).

Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed in women treated with estrogens-alone therapy that is substantially lower than that found in users of estrogen-progestogen combinations (see Section 4.8 Adverse effects (undesirable effects), Description of selected adverse reactions, Breast cancer risk). The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment.

### **Ovarian cancer**

The effect of DUAVIVE on the risk of ovarian cancer is unknown.

Ovarian cancer is much rarer than breast cancer. Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking estrogen-only HRT, which becomes apparent within 5 years of use and diminishes over time after stopping. Some other studies, including the WHI trial, suggest that use of combined HRTs may be associated with a similar or slightly smaller risk (see Section 4.8 Adverse effects (undesirable effects), Description of selected adverse reactions, Ovarian cancer).

### **Venous thromboembolism (VTE)**

In clinical trials of up to 2 years duration in postmenopausal women with CE/bazedoxifene, cases of VTE have been reported (see Section 4.8 Adverse effects (undesirable effects), Description of selected adverse reactions, Risk of venous thromboembolism). Should a VTE event occur or be suspected, DUAVIVE should be discontinued immediately.

SERMs (including bazedoxifene) and estrogens individually increase the risk of VTE (see Section 4.8 Adverse effects (undesirable effects), Description of selected adverse reactions, Risk of venous thromboembolism).

Hormone Replacement Therapy (HRT) is associated with a 1.3-3 fold risk of developing VTE. The occurrence of such an event is more likely in the first year of HRT than later (see Section 4.8 Adverse effects (undesirable effects), Description of selected adverse reactions, Risk of venous thromboembolism).

Patients with known thrombophilic states have an increased risk of VTE and hormone therapy may add to this risk. DUAVIVE is contraindicated in these patients (see Section 4.3 Contraindications).

Generally recognised risk factors for VTE include, use of estrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m<sup>2</sup>), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE. As in all postoperative patients, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery temporarily stopping DUAVIVE 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised. In addition, women taking DUAVIVE should be advised to move about periodically during travel involving prolonged immobilisation.

In women with no personal history of VTE but with a first-degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening). If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g., antithrombin, protein S, or protein C deficiencies or a combination of defects) hormone therapy is contraindicated.

Women already on chronic anticoagulant treatment require careful consideration of the benefit risk of use of hormone therapy.

If VTE develops after initiating therapy, or is suspected, DUAVIVE should be discontinued immediately. Women should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g., painful swelling of a leg, sudden pain in the chest, dyspnoea).

### **Coronary artery disease (CAD)**

The effect of DUAVIVE on the risk of CAD is unknown.

There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received estrogen-only therapy. Randomised controlled data found no increased risk of CAD in hysterectomised women using estrogen-only therapy.

### **Stroke**

The effect of DUAVIVE on the risk of stroke is unknown.

Estrogen-only therapy is associated with an up to 1.5-fold increase in risk of stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see Section 4.8 Adverse effects (undesirable effects), Description of selected adverse reactions, Risk of stroke).

Should a stroke occur or be suspected, DUAVIVE should be discontinued immediately (see Section 4.3 Contraindications).

### **Visual abnormalities**

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilloedema or retinal vascular lesions, DUAVIVE should be permanently discontinued.

### **Gallbladder disease**

Cases (<1%) of cholecystitis have been reported in CE/bazedoxifene clinical trials. A 2 to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported (see Section 4.8 Adverse effects (undesirable effects)).

### **Elevated blood pressure**

In a small number of case reports in women receiving estrogens, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomised,

placebo-controlled clinical study, a generalised effect of estrogens on blood pressure was not seen.

### **Hypertriglyceridaemia**

Women with pre-existing hypertriglyceridaemia should be followed closely during treatment with estrogens, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition. CE/bazedoxifene has not been studied in women with baseline triglyceride levels >3.4 mmol/L. In clinical trials of up to 2 years duration, CE/bazedoxifene was associated with an increase from baseline in the concentration of serum triglycerides of approximately 16% at month 12 and 20% at month 24. Annual monitoring of serum triglyceride levels should therefore be considered.

### **Impaired liver function and past history of cholestatic jaundice**

CE/bazedoxifene has not been studied in patients with impaired liver function or history of cholestatic jaundice. Estrogens may be poorly metabolised in women with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, DUAVIVE should be discontinued (see Sections 4.2 Dose and method of administration, Dosage Adjustment, Hepatic impairment and 5.2 Pharmacokinetic properties, Hepatic impairment).

### **Fluid retention**

Estrogens may cause fluid retention, and therefore patients with cardiac or renal impairment should be carefully monitored when being treated with DUAVIVE, since it is expected that the level of circulating estrogens components of DUAVIVE will be increased. Use in this population is not recommended (see Sections 4.2 Dose and method of administration, Dosage Adjustment, Renal impairment and 5.2 Pharmacokinetic properties, Renal impairment).

### **Dementia**

The effect of DUAVIVE on the risk of dementia is unknown.

Estrogen therapy use does not improve cognitive function. The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of probable dementia in women who start using continuous estrogen-only therapy after the age of 65.

### **Hypothyroidism**

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

### **Hypocalcemia**

Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcaemia may occur.

## **Hereditary and acquired angioedema**

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary and acquired angioedema.

## **Other conditions**

DUAVIVE contains lactose, sucrose, glucose (in the polydextrose and maltitol liquid components of Opaglos 2 Clear) and sorbitol (in the polydextrose component of Opaglos 2 Clear). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

## **Use in hepatic impairment**

The safety and efficacy of CE/bazedoxifene have not been evaluated in patients with hepatic impairment. Use in this population is contraindicated (see Sections 4.4 Special warnings and precautions for use, Impaired liver function and past history of colestic jaundice and 5.2 Pharmacokinetic properties, Hepatic impairment).

## **Use in renal impairment**

The pharmacokinetics of CE/bazedoxifene have not been evaluated in patients with renal impairment. Use in this population is, therefore, not recommended (see Section 5.2 Pharmacokinetic properties, Renal impairment).

Patients with renal impairment should be closely monitored since it is expected that the level of circulating estrogens components of DUAVIVE will be increased. Use in this population is not recommended (see Sections 4.2 Dosage and method of administration, Dosage adjustment, Renal impairment and 5.2 Pharmacokinetic properties, Renal impairment).

## **Use in the elderly**

DUAVIVE has not been studied in women over 75 years of age. Of the total number of women in Phase 3 clinical trials who received CE/bazedoxifene 20 mg, 2.4% (n=77) were aged  $\geq 65$  years. No overall differences in safety or effectiveness were observed between women aged  $>65$  years and younger women, but greater sensitivity of some older individuals cannot be ruled out (see Section 5.2 Pharmacokinetic properties, Elderly).

## **Paediatric use**

There is no relevant use of DUAVIVE in the paediatric population.

## **Effects on laboratory tests**

Estrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered.

Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1 antitrypsin, ceruloplasmin).

## 4.5 Interactions with other medicines and other forms of interactions

Results from a clinical drug-drug interaction study conducted with DUAVIVE and from interaction studies with CE or bazedoxifene monotherapy are summarised below.

### Cytochrome P450

*In vitro* and *in vivo* studies have shown that estrogens are partially metabolised by cytochrome P450 enzymes, including CYP3A4. However, in a clinical drug-drug interaction study, repeat administration of 200 mg itraconazole, a strong CYP3A4 inhibitor, had minimal impact on the pharmacokinetics of CE (as measured by estrone and equilin) and bazedoxifene when administered with a single dose of CE 0.45 mg/bazedoxifene 20 mg.

The metabolism of estrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, such as anticonvulsants (e.g., phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g., rifampicin, rifabutin, nevirapine, efavirenz). Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St John's wort (*Hypericum perforatum*) may induce the metabolism of estrogens. Clinically, an increased metabolism of estrogens may lead to decreased effect and changes in the uterine bleeding profile.

Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, ritonavir and grapefruit juice, may increase plasma concentrations of estrogens and may result in adverse reactions.

Bazedoxifene undergoes little or no cytochrome P450 (CYP)-mediated metabolism. Bazedoxifene does not inhibit the activities of major CYP isoenzymes at clinically relevant systemic concentrations. Bazedoxifene does not induce the activities of the major CYP isoenzymes.

### Uridine diphosphate glucuronosyltransferase (UGT)

Bazedoxifene undergoes metabolism by UGT enzymes in the intestinal tract, kidney and liver (see Section 5.2 Pharmacokinetic properties). The metabolism of bazedoxifene may be increased by concomitant use of substances known to induce UGTs, such as rifampicin, phenobarbital, carbamazepine, and phenytoin, potentially leading to decreased systemic concentrations of bazedoxifene. A reduction in bazedoxifene exposure 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 endometrial biopsy to exclude endometrial malignancy (see Section 4.4 Special warnings and precautions for use).

### Ibuprofen

The pharmacokinetics of bazedoxifene and ibuprofen are not significantly altered when the drugs are co-administered.

### Atorvastatin

Concomitant administration of bazedoxifene (40 mg daily) and atorvastatin (20 mg, single-dose) to healthy postmenopausal women did not affect the pharmacokinetics of bazedoxifene, atorvastatin or its active metabolites.

## **Azithromycin**

The pharmacokinetics of bazedoxifene were not significantly altered when co-administered with azithromycin.

## **Aluminium and magnesium hydroxide**

There was no clinically relevant pharmacokinetic interaction of antacids containing aluminium and magnesium hydroxide with bazedoxifene.

## **Drugs highly bound to plasma proteins**

Based on *in vitro* bazedoxifene plasma protein-binding characteristics, interactions with warfarin, digoxin or diazepam are unlikely.

## **4.6 Fertility, pregnancy and lactation**

### **Effects on fertility**

Fertility studies with CE/bazedoxifene have not been conducted. The following data are based on the findings in studies with bazedoxifene.

Female rats were administered oral daily dosages of 0.3 to 30 mg/kg (yielding 0.03 to 10 times the plasma AUC in patients at the maximum recommended human dose of 20 mg/day) prior to and during mating with untreated males. Estrous cycles and fertility were adversely affected in all bazedoxifene-treated female groups. The potential risk for humans is unknown.

### **Use in pregnancy – Pregnancy Category D**

DUAVIVE is only for use in postmenopausal women, and is contraindicated in women who are or may become pregnant (see Section 4.3 Contraindications). There are no data from the use of DUAVIVE in pregnant women. If pregnancy occurs during treatment with DUAVIVE, it should be withdrawn immediately.

Treatment of pregnant rats with bazedoxifene at oral doses  $\geq 1$  mg/kg/day (yielding  $\geq 0.3$  times the human exposure based on plasma AUC) resulted in increased post-implantation loss, reduced numbers of live fetuses, reduced fetal weight, increased fetal vascular variations and impaired fetal ossification. In rabbit studies with bazedoxifene, abortion and increased incidences of fetal heart malformation (ventricular septal defect) and fetal skeletal system anomalies (ossification delays, misshapen or misaligned bones, primarily of the skull and spine) were observed at oral doses  $\geq 0.5$  mg/kg/day ( $\geq 1.7$  times the human exposure). Adverse effects on embryofetal development in animals occurred at maternally toxic doses but at exposure levels below or only slightly above that of patients. The animal studies suggest a potential risk to the human fetus.

### **Use in lactation**

DUAVIVE is contraindicated during breast-feeding (see Section 4.3 Contraindications). It is not known whether bazedoxifene is excreted in human milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving CE. Estrogen administration to breast-feeding mothers has been shown to decrease the quantity and quality of the milk.

## 4.7 Effects on ability to drive and use machines

DUAVIVE has a minor influence on the ability to drive and use machines.

In clinical trials with bazedoxifene monotherapy, somnolence was reported as an adverse reaction, and patients should be advised on the potential effect on driving and using machines.

In patients receiving bazedoxifene monotherapy there have been post-marketing reports of visual symptoms such as visual acuity disturbance or blurred vision. If such symptoms occur, patients should avoid driving or use of machines that requires accurate visual perception until symptoms have resolved, or until they have received medical advice that it is safe to do so (see Section 4.8 Adverse effects (undesirable effects), Post-marketing experience).

## 4.8 Adverse effects (undesirable effects)

The safety of CE/bazedoxifene was evaluated in 4,868 post-menopausal women who participated in the five Phase 3 trials. Among these, 1,585 women were treated with CE 0.45 mg/bazedoxifene 20 mg and 1,241 received placebo. Long-term exposure to CE/bazedoxifene for up to 2 years was evaluated; 3,322 women were exposed to CE/bazedoxifene for at least 1 year, and 1,999 women were exposed for 2 years.

In the five Phase 3 placebo-controlled, randomised clinical trials, 8.4% of the 3,168 women treated with CE/bazedoxifene discontinued treatment due to an adverse event, compared with 10.2% of the 1,241 women who received placebo. The most common reasons leading to discontinuation were abdominal pain and nausea in the treatment arms and continuing hot flushes in the placebo arms.

Table 1 below lists the adverse events (regardless of causality) occurring in  $\geq 1\%$  of women treated with DUAVIVE in double-blind, placebo-controlled Phase 3 studies of up to 2 years duration.

**Table 1: Adverse Events (regardless of causality) with an Incidence Exceeding the Placebo Rate Reported by  $\geq 1\%$  of Patients in Placebo-Controlled Phase 3 trials of DUAVIVE**

<b>System Organ Class Preferred term</b>	<b>CE 0.45/BZA 20* n=1585</b>	<b>CE 0.45/BZA 20 &amp; CE 0.625/BZA 20 n=3168</b>	<b>Placebo n=1241</b>
Any adverse event	1334 (84.2)	2676 (84.5)	1053 (84.9)
<b><i>Cardiac disorders</i></b>			
Palpitations	24 (1.5)	37 (1.2)	17 (1.4)
Tachycardia	16 (1.0)	20 (0.6)	10 (0.8)
<b><i>Ear and labyrinth disorders</i></b>			
Ear Pain	16 (1.0)	35 (1.1)	13 (1.0)
Vertigo	32 (2.0)	68 (2.1)	19 (1.5)
<b><i>Gastrointestinal disorders</i></b>			
Abdominal discomfort	30 (1.9)	59 (1.9)	16 (1.3)
Abdominal pain	89 (5.6)	183 (5.8)	58 (4.7)
Abdominal pain lower	25 (1.6)	45 (1.4)	13 (1.0)

<b>System Organ Class Preferred term</b>	<b>CE 0.45/BZA 20* n=1585</b>	<b>CE 0.45/BZA 20 &amp; CE 0.625/BZA 20 n=3168</b>	<b>Placebo n=1241</b>
Abdominal pain upper	100 (6.3)	189 (6.0)	53 (4.3)
Constipation	74 (4.7)	150 (4.7)	55 (4.4)
Diarrhoea	107 (6.8)	186 (5.9)	67 (5.4)
Dyspepsia	90 (5.7)	163 (5.1)	67 (5.4)
Gastroesophageal reflux disease	29 (1.8)	51 (1.6)	22 (1.8)
Nausea	118 (7.4)	208 (6.6)	60 (4.8)
Toothache	65 (4.1)	117 (3.7)	45 (3.6)
Vomiting	49 (3.1)	86 (2.7)	33 (2.7)
<b><i>General disorders and administration site conditions</i></b>			
Fatigue	56 (3.5)	109 (3.4)	43 (3.5)
Non-cardiac chest pain	20 (1.3)	35 (1.1)	11 (0.9)
Pain	61 (3.8)	125 (3.9)	49 (3.9)
<b><i>Immune system disorders</i></b>			
Hypersensitivity	24 (1.5)	52 (1.6)	17 (1.4)
Seasonal allergy	33 (2.1)	66 (2.1)	22 (1.8)
<b><i>Infections and infestations</i></b>			
Bronchitis	43 (2.7)	86 (2.7)	31 (2.5)
Cystitis	26 (1.6)	56 (1.8)	19 (1.5)
Gastroenteritis viral	32 (2.0)	61 (1.9)	12 (1.0)
Influenza	161 (10.2)	298 (9.4)	122 (9.8)
Nasopharyngitis	248 (15.6)	480 (15.2)	154 (12.4)
Pneumonia	14 (0.9)	32 (1.0)	13 (1.0)
Upper respiratory tract infection	120 (7.6)	238 (7.5)	90 (7.3)
Urinary tract infection	91 (5.7)	170 (5.4)	71 (5.7)
Vulvovaginal mycotic infection	37 (2.3)	83 (2.6)	9 (0.7)
<b><i>Injury, poisoning and procedural complications</i></b>			
Arthropod bite	22 (1.4)	37 (1.2)	6 (0.5)
<b><i>Investigations</i></b>			
Blood pressure increased	17 (1.1)	46 (1.5)	16 (1.3)
Blood triglycerides increased	34 (2.1)	58 (1.8)	18 (1.5)
Smear cervix abnormal	22 (1.4)	44 (1.4)	16 (1.3)
<b><i>Metabolism and nutrition disorders</i></b>			
Hypertriglyceridaemia	29 (1.8)	56 (1.8)	20 (1.6)
<b><i>Musculoskeletal and connective tissue disorders</i></b>			
Arthritis	16 (1.0)	34 (1.1)	13 (1.0)
Back pain	226 (14.3)	482 (15.2)	171 (13.8)
Muscle spasms	137 (8.6)	252 (8.0)	70 (5.6)

<b>System Organ Class Preferred term</b>	<b>CE 0.45/BZA 20* n=1585</b>	<b>CE 0.45/BZA 20 &amp; CE 0.625/BZA 20 n=3168</b>	<b>Placebo n=1241</b>
Musculoskeletal chest pain	24 (1.5)	39 (1.2)	9 (0.7)
Musculoskeletal stiffness	22 (1.4)	46 (1.5)	19 (1.5)
Myalgia	130 (8.2)	249 (7.9)	99 (8.0)
Neck pain	71 (4.5)	136 (4.3)	53 (4.3)
Tendonitis	10 (0.6)	32 (1.0)	6 (0.5)
<b><i>Nervous system disorders</i></b>			
Dizziness	69 (4.4)	130 (4.1)	40 (3.2)
Hypoaesthesia	17 (1.1)	29 (0.9)	9 (0.7)
Sinus headache	65 (4.1)	108 (3.4)	31 (2.5)
<b><i>Renal and urinary disorders</i></b>			
Dysuria	20 (1.3)	36 (1.1)	13 (1.0)
<b><i>Reproductive system and breast disorders</i></b>			
Breast pain	52 (3.3)	92 (2.9)	22 (1.8)
Breast tenderness	26 (1.6)	46 (1.5)	17 (1.4)
Pelvic pain	15 (0.9)	36 (1.1)	14 (1.1)
Vaginal discharge	26 (1.6)	63 (2.0)	20 (1.6)
Vulvovaginal pruritus	20 (1.3)	41 (1.3)	14 (1.1)
<b><i>Respiratory, thoracic and mediastinal disorders</i></b>			
Cough	91 (5.7)	183 (5.8)	69 (5.6)
Dyspnoea	13 (0.8)	32 (1.0)	8 (0.6)
Nasal congestion	49 (3.1)	82 (2.6)	25 (2.0)
Oropharyngeal pain	69 (4.4)	131 (4.1)	50 (4.0)
Pharyngolaryngeal pain	28 (1.8)	64 (2.0)	19 (1.5)
Rhinitis allergic	16 (1.0)	26 (0.8)	10 (0.8)
Rhinorrhoea	14 (0.9)	36 (1.1)	12 (1.0)
Sinus congestion	43 (2.7)	92 (2.9)	26 (2.1)
<b><i>Skin and subcutaneous tissue disorders</i></b>			
Acne	17 (1.1)	27 (0.9)	10 (0.8)
Alopecia	31 (2.0)	60 (1.9)	13 (1.0)
Dermatitis contact	22 (1.4)	40 (1.3)	10 (0.8)
Dry skin	18 (1.1)	35 (1.1)	6 (0.5)
Pruritus	30 (1.9)	60 (1.9)	16 (1.3)
Rash	42 (2.6)	92 (2.9)	25 (2.0)
<b><i>Vascular disorders</i></b>			
Hypertension	61 (3.8)	111 (3.5)	45 (3.6)

\*approved strength.

### **Adverse reactions observed with CE/bazedoxifene**

Table 2 below lists the adverse reactions observed with both CE 0.45 mg/bazedoxifene 20 mg and CE 0.625 mg/bazedoxifene 20 mg treatment groups (n=3,168) in placebo controlled

clinical trials. Adverse reactions were categorised as very common, common, uncommon or rare.

**Table 2: Adverse Reactions Observed with CE/bazedoxifene**

System organ class	Frequency of occurrence of adverse reactions			
	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
<i>Infections and infestations</i>		Vulvovaginal candidiasis		
<i>Vascular disorders</i>				Venous thromboembolic events (including, pulmonary embolism, retinal vein thrombosis, deep vein thrombosis and thrombophlebitis)
<i>Gastrointestinal disorders</i>	Abdominal pain	Constipation, Diarrhoea, Nausea		
<i>Hepatobiliary disorders</i>			Cholecystitis	
<i>Musculoskeletal and connective tissue disorders</i>		Muscle spasms		
<i>Investigations</i>		Blood triglycerides increased		

### Description of selected adverse reactions

#### ***Breast cancer risk***

Breast cancer risk associated with the use of estrogens alone is represented by several studies. Any increased risk to users of estrogen-only therapy is substantially lower than that seen in users of estrogen-progestogen combinations. The level of risk is dependent on duration of use (see Section 4.4 Special warnings and precautions for use). Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (Million Women Study) are presented in Table 3 and Table 4.

**Table 3: US WHI Estrogen Only (ET) Arm – Additional Risk of Breast Cancer After 5 Years Use**

Age range (years)	Incidence per 1,000 women in placebo arm over 5 years	Risk ratio & 95% CI	Additional cases per 1,000 ET users over 5 years (95% CI)
CE Estrogen only			
50-79	21	0.8 (0.7-1.0)	-4 (-6 – 0)*

\*WHI study in women with no uterus, which did not show an increase in risk of breast cancer.

**Table 4: Million Women Study (Estradiol Only Arm) – Estimated Additional Risk of Breast Cancer after 5 Years Use**

Age range (years)	Additional cases per 1,000 never-users of HRT over a 5 year period*	Risk ratio <sup>#</sup>	Additional cases per 1,000 ET users over 5 years (95%CI)
Estradiol only			
50-65	9-12	1.2	1-2 (0-3)

\*Taken from baseline incidence rates in developed countries.

<sup>#</sup>Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use.

### ***Endometrial cancer risk***

#### *Postmenopausal women with a uterus*

In women with a uterus, use of estrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see Sections 4.4 Special warnings and precautions for use, Endometrial hyperplasia and carcinoma and 5.1 Pharmacodynamic properties, Clinical trials, Effect on the endometrium). Depending on the duration of estrogen-only use and estrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from 5 to 55 extra cases diagnosed in every 1,000 women between the ages of 50 and 65 years.

DUAVIVE contains bazedoxifene, which reduces the risk of endometrial hyperplasia that can occur with estrogen-only use (see Sections 4.4 Special warnings and precautions for use, Endometrial hyperplasia and carcinoma and 5.1 Pharmacodynamic properties, Clinical trials, Effect on the endometrium) Endometrial hyperplasia may be a precursor to endometrial cancer.

### ***Ovarian cancer***

Use of estrogen-only HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see Section 4.4 Special warnings and precautions for use).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2,000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2,000 will be diagnosed with ovarian cancer over a 5-year period.

### ***Risk of venous thromboembolism(VTE)***

In the bazedoxifene osteoporosis treatment trial (mean age = 66.5 years), the VTE rate per 1,000 women-years through the 3-year study period was 2.86 in the bazedoxifene (20 mg) group and 1.76 in the placebo group and through the 5-year study period was 2.34 in the bazedoxifene 20 mg group and 1.56 in the placebo group. After 7 years, the VTE rate per 1,000 women-years was 2.06 in the bazedoxifene 20 mg group and 1.36 in the placebo group.

Estrogens are known to increase the risk of VTE (see Section 4.4 Special warnings and precautions for use, Venous thromboembolism). The occurrence of such a reaction is more likely in the first year of treatment. The data from the largest randomised trial are summarised below in Table 5.

**Table 5: WHI Studies Estrogen Only Arm – Additional Risk of VTE Over 5 Years Use**

<b>Age range (years)</b>	<b>Incidence per 1,000 women in placebo arm over 5 years</b>	<b>Risk ratio &amp; 95%CI</b>	<b>Additional cases per 1,000 ET users</b>
Oral estrogen-only*			
50-59	7	1.2 (0.6-2.4)	1 (-3-10)

\*study in women with no uterus.

### ***Risk of stroke***

The use of estrogen-only therapy is associated with an up to 1.5 fold increased relative risk of stroke. This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use estrogen therapy will increase with age (see Section 4.4 Special warnings and precautions for use, stroke). The additional risk of stroke over five years of use was assessed in the largest randomised trial in women without a uterus (WHI) from 50-59 years of age (see Table 6).

**Table 6: WHI Studies Combined – Additional Risk of Stroke\* Over 5 Years Use**

<b>Age range (years)</b>	<b>Incidence per 1,000 women in placebo arm over 5 years</b>	<b>Risk ratio &amp; 95%CI</b>	<b>Additional cases per 1,000 HRT users over 5 years</b>
50-59	8	1.3 (1.1-1.6)	3 (1-5)

\*no differentiation was made between ischaemic and haemorrhagic stroke.

### **Post-marketing experience**

In patients receiving bazedoxifene monotherapy there have been post-marketing reports of ocular events other than retinal vein thrombosis. These reports include visual acuity reduced, blurred vision, photopsia, visual field defect, visual impairment, dry eye, eyelid oedema, blepharospasm, eye pain and eye swelling. The underlying nature of these events is uncertain. If ocular symptoms occur, patients should be advised to seek medical attention.

Hereditary and acquired angioedema.

## Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## 4.9 Overdose

In case of overdose of DUAVIVE, there is no specific antidote, and the treatment should reflect the symptoms.

Symptoms of overdose of estrogen-containing medicinal products in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue; withdrawal bleeding may occur in females.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

#### Mechanism of action

DUAVIVE pairs CE with the selective estrogen receptor modulator (SERM), bazedoxifene; this pairing is defined as a tissue selective estrogen complex (TSEC). The active ingredients of CE are primarily the sulfate esters of estrone, equilin sulfates and 17 $\alpha$ / $\beta$ -estradiol which demonstrate tissue selective estrogen receptor agonist activity. These substitute for the loss of estrogen production in menopausal women, and alleviate menopausal symptoms. As estrogens promote the growth of the endometrium, unopposed estrogens increase the risk of endometrial hyperplasia and cancer. The addition of bazedoxifene, acting as an estrogen receptor antagonist in the uterus, greatly reduces the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

#### Clinical trials

The safety and efficacy of CE/bazedoxifene as a treatment for moderate to severe vasomotor symptoms (VMS) associated with menopause was established in a randomised, double-blind, placebo-controlled study. The Selective Estrogens, Menopause, and Response to Therapy (SMART) 2 trial enrolled a total of 318 women, age 42-64 (mean age of 53 years), who had at least 7 moderate to severe hot flushes per day or at least 50 per week at baseline. The mean number of years since menopause was 4.5 years with all women undergoing natural menopause. A total of 127 women were assigned to CE 0.45 mg/bazedoxifene 20 mg and 63 women were assigned to placebo.

In the SMART 2 trial, CE 0.45 mg/bazedoxifene 20 mg significantly reduced the number and severity of moderate to severe hot flushes, as measured by the daily severity score, compared with placebo at Weeks 4 and 12. The change from baseline in the number and severity of moderate to severe hot flushes observed and the difference from placebo are shown in Table 7.

**Table 7: Adjusted Mean Change from Baseline in the Average Daily Frequency and Severity of Hot Flashes**

	Frequency		Severity	
	CE 0.45 mg/ bazedoxifene 20 mg	Placebo	CE 0.45 mg/ bazedoxifene 20 mg	Placebo
N	122	63	122	63
Baseline	10.3	10.5	2.3	2.3
<b>Week 4</b>				
Mean Change <sup>1</sup>	-5.9	-2.8	-0.6	-0.1
Treatment Difference <sup>2</sup>	-3.1 (-4.4, -1.7)*	--	-0.5 (-0.7, -0.3)*	--
<b>Week 12</b>				
Mean Change <sup>1</sup>	-7.6	-4.9	-0.9	-0.3
Treatment Difference <sup>2</sup>	-2.7 (-3.8, -1.6)*	--	-0.6 (-0.9, -0.4)*	--
*p<0.001				
<sup>1</sup> Change from baseline using ANCOVA model				
<sup>2</sup> Based on raw data analysis using ANCOVA model: Difference= Treatment + Baseline + Site				

***Effects on the endometrium***

Effects of CE/bazedoxifene on endometrial hyperplasia and endometrial malignancy were assessed in SMART 1, a 24-month, double-blind, randomised, placebo- and active-controlled trial and SMART 5, a 12-month, double-blind, randomised, placebo- and active-controlled trial. The Efficacy Evaluable population included patients who had taken at least one dose of CE/Bazedoxifene, had baseline and post baseline endometrial biopsies, or had been diagnosed with hyperplasia. The incidence of endometrial hyperplasia for CE/bazedoxifene was below 1% in both trials (see Table 8).

**Table 8: Incidence of Endometrial Hyperplasia at Month 12 and Month 24**

Treatment Group	Month	SMART 1*		SMART 5*	
		% (n/N)	1 – Sided 95% UL	% (n/N)	1 – Sided 95% UL
CE 0.45 mg/BZA 20 m	12	0.00% (0/336)	0.89	0.30% (1/335)	1.41
	24	0.68% (2/294)	2.13	--	--
UL = Upper limit					
* = Efficacy Evaluable population					

***Effects on uterine bleeding or spotting***

Cumulative amenorrhoea (uterine bleeding or spotting) was a key secondary endpoint evaluated in two clinical trials (SMART 1 and SMART 5). In SMART 1, cumulative amenorrhoea at Year 1 was 83% and 85% in women treated with CE 0.45 mg/bazedoxifene 20 mg and placebo respectively. In SMART 5, cumulative amenorrhoea at Year 1 was 88% in

women treated with CE 0.45 mg/bazedoxifene 20 mg, 82% with bazedoxifene 20 mg and 84% in women who received placebo. For women treated with CE 0.45 mg/medroxyprogesterone 1.5 mg, the cumulative amenorrhoea was 54%.

### ***Effects on breast***

#### ***Breast pain***

The effect of CE/bazedoxifene on breast pain was evaluated as a key secondary endpoint in SMART 1, 2 and 5. In SMART 1, the rates for CE 0.45 mg/bazedoxifene 20 mg and placebo were 9% and 6% respectively. The rates in SMART 2 were 10% and 5% respectively and in SMART 5, the rates were 6% and 5% respectively. For bazedoxifene 20 mg, the breast pain rate was 7%. In SMART 5, the rate for CE 0.45 mg/medroxyprogesterone acetate 1.5 mg was 24%.

#### ***Breast density***

The effect of CE/bazedoxifene on mammographic density was a key secondary endpoint in the SMART 1 and SMART 5 studies.

In SMART 5, the change in mammographic density in postmenopausal women (mean age=54 years) treated with CE 0.45 mg/bazedoxifene 20 mg (n=186) or bazedoxifene 20 mg (n=97) was not different from placebo (n=181). In women treated with CE 0.45 mg/medroxyprogesterone 1.5 mg (n=68), mammographic density was increased compared to placebo. Supplemental evaluation of mammograms from the SMART 1 trial yielded results consistent with SMART 5.

In an ancillary study, mammographic breast density changes at 2 years for the bazedoxifene 20 mg group were (-1.45 percentage points,) while no changes were observed in the placebo group (-0.15 percentage points).

### ***Effects on bone mineral density (BMD)***

BMD changes at the lumbar spine was a key secondary endpoint, assessed in the SMART 5 study. In this study, women treated with CE 0.45 mg/bazedoxifene 20 mg showed a change from baseline in lumbar spine BMD (+1.52%) at Month 12 compared to placebo. In the same study, the change in BMD with bazedoxifene 20 mg alone and CE 0.45 mg/medroxyprogesterone 1.5 mg was +1.35%, +2.58%, respectively.

## **5.2 Pharmacokinetic properties**

Pharmacokinetic studies for CE/bazedoxifene were conducted in healthy postmenopausal women who were naturally postmenopausal or who had undergone bilateral oophorectomy.

Following multiple doses of CE 0.45 mg/bazedoxifene 20 mg, the mean steady state pharmacokinetic parameters for CE (baseline adjusted for total estrone) and bazedoxifene are summarised in Table 9.

**Table 9: Mean ± SD Steady-State (ss) Pharmacokinetic Parameters (n=24)**

	<b>C<sub>max</sub> (ng/mL)</b>	<b>T<sub>max</sub> (hr)</b>	<b>AUC<sub>ss</sub> (ng·hr/mL)</b>
Bazedoxifene	6.9 ± 3.9	2.5 ± 2.1	71 ± 34
Baseline-adjusted total estrone	2.6 ± 0.8	6.5 ± 1.6	35 ± 12

C<sub>max</sub> – maximum observed concentration.

t<sub>max</sub> – time to C<sub>max</sub>.

AUC – area under the concentration-time curve from time 0 to 24 hours.

### **Absorption**

After a single dose of CE/bazedoxifene, bazedoxifene and baseline-adjusted total estrone were absorbed with a t<sub>max</sub> of approximately 2 hours and 8.5 hours, respectively. When single doses of CE 0.625 mg/bazedoxifene 20 mg were administered with a high-fat meal, bazedoxifene C<sub>max</sub> was unaffected, but AUC increased by approximately 25%. Food had little or no effect on the exposure of CE.

CE/bazedoxifene can be administered with or without food.

Following administration of bazedoxifene alone, a linear increase in plasma concentrations for single doses from 0.5 mg up to 120 mg and multiple daily doses from 1 mg to 80 mg was observed. The absolute bioavailability of bazedoxifene is approximately 6%.

CE are soluble in water and are well-absorbed from the gastrointestinal tract after release from the medicinal product formulation. Estrogen dose proportionality was assessed in two studies of CE. Dose-proportional increases in both AUC and C<sub>max</sub> were observed across the dose range from 0.3 mg to 0.625 mg of CE for total (conjugated plus unconjugated) equilin, total estrone adjusted for baseline, and unconjugated estrone adjusted for baseline.

### **Distribution**

The distribution of CE and bazedoxifene after administration of CE/bazedoxifene has not been studied.

Following intravenous administration of a 3 mg dose of bazedoxifene alone, the volume of distribution is 14.7 ± 3.9 L/kg. Bazedoxifene is highly bound (approximately 99%) to plasma proteins at therapeutic concentrations *in vitro*, but does not appear to bind to sex hormone binding globulin (SHBG).

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to SHBG and albumin.

### **Metabolism**

The metabolic disposition of CE and bazedoxifene, after administration of CE/bazedoxifene, has not been studied.

Exogenous estrogens are metabolised in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. 17β-estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. In postmenopausal women, a significant proportion of the circulating

estrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

The metabolic disposition of bazedoxifene in postmenopausal women has been determined following oral administration of 20 mg of radiolabelled bazedoxifene. Bazedoxifene is extensively metabolised in women. Glucuronidation is the major metabolic pathway. *In vitro* studies indicated that this occurs in the liver, kidney and intestines, and principally involves UGT1A1 and UGT1A10 with a smaller role for UGT1A9. Little or no cytochrome P450-mediated metabolism is evident. Bazedoxifene-5-glucuronide is the major circulating metabolite, and retains some pharmacological activity. The concentrations of this glucuronide are approximately 10-fold higher than those of unchanged bazedoxifene in plasma.

### **Excretion**

After a single dose of CE/bazedoxifene, baseline-adjusted total estrone (representing CE) is eliminated with a half-life of approximately 17 hours. Bazedoxifene is eliminated with a half-life of approximately 30 hours. Steady-state concentrations are achieved by the second week of once-daily administration.

CE components, 17 $\beta$ -estradiol, estrone, and estriol are excreted in the urine, along with glucuronide and sulfate conjugates.

The clearance of bazedoxifene is  $0.4 \pm 0.1$  L/h/kg based on IV administration. The major route of excretion of radiolabelled bazedoxifene is the faeces, and less than 1% of the dose is eliminated in urine.

### **Renal impairment**

The pharmacokinetics of CE/bazedoxifene have not been evaluated in patients with renal impairment.

No pharmacokinetic trials for CE were conducted in specific populations, including women with renal impairment.

Limited clinical data (n=5) for bazedoxifene are available in subjects with moderate renal impairment (creatinine clearance <50 mL/min). A single 20 mg dose of bazedoxifene was administered to these subjects. Negligible (<1%) amounts of bazedoxifene are eliminated in urine. Impaired renal function showed little or no influence on bazedoxifene pharmacokinetics.

### **Hepatic impairment**

The pharmacokinetics of CE/bazedoxifene have not been evaluated in women with hepatic impairment or past history of cholestatic jaundice.

No pharmacokinetic trials for CE were conducted in specific populations, including women with hepatic impairment

The disposition of a single 20 mg dose of bazedoxifene was compared in women with hepatic impairment (Child-Pugh Class A [n=6], B [n=6], and C [n=6]) and women with normal hepatic function (n=18). On average, women with hepatic impairment showed a 4.3-fold increase in AUC compared with controls. Safety and efficacy have not been evaluated further in women with hepatic insufficiency. Use of CE/bazedoxifene in this population is contraindicated (see Sections 4.2 Dose and method of administration, Dosage adjustments, Hepatic

impairment, 4.3 Contraindications and 4.4 Special warnings and precautions for use, Impaired liver function and past history of cholestatic jaundice).

### **Elderly**

The pharmacokinetics of CE/bazedoxifene have not been evaluated in women over 75 years of age.

No pharmacokinetic trials for CE were conducted in specific populations, including women over 75 years of age.

The pharmacokinetics of a 20 mg single dose of bazedoxifene were evaluated in a study in 26 healthy postmenopausal women. On average, compared to women 51 to 64 years of age (n=8), women 65 to 74 years of age (n=8) showed a 1.5-fold increase in AUC, and women >75 years of age (n=8) showed a 2.6-fold increase in AUC. This increase is most likely attributable to age-related changes in hepatic function.

### **Paediatric use**

The pharmacokinetics of CE/bazedoxifene have not been evaluated in a paediatric population.

### **Body mass index (BMI)**

In a clinical study, BMI was shown to have minimal impact on the relative systemic exposures of CE and bazedoxifene. A single dose of CE 0.45 mg/bazedoxifene 20 mg was administered to 12 obese (BMI  $\geq 30$  kg/m<sup>2</sup>) and 12 non-obese (BMI  $< 30$  kg/m<sup>2</sup>) postmenopausal women. In obese subjects, the systemic exposures of baseline-adjusted total estrone, total equilin, and bazedoxifene were 21%, 32%, and 13% lower, respectively, compared to non-obese subjects.

## **5.3 Preclinical safety data**

### **Genotoxicity**

Genotoxicity studies with CE/bazedoxifene have not been conducted. The following data are based on the findings in studies with bazedoxifene.

Bazedoxifene was not genotoxic *in vitro* in assays for bacterial reverse mutation, mammalian forward mutation in mouse lymphoma cells, and for chromosomal aberrations in Chinese hamster ovary (CHO) cells, or *in vivo* in the mouse micronucleus assay.

### **Carcinogenicity**

Carcinogenicity studies with CE/bazedoxifene have not been conducted.

Long-term, continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina and liver.

In 6-month oral carcinogenicity studies in transgenic Tg.rasH2 mice, bazedoxifene increased the incidence of benign, ovarian granulosa-cell tumours in female mice given 150 or 500 mg/kg/day. Systemic exposure (AUC) to bazedoxifene in these groups was approximately 40 and 110 times that in postmenopausal women at the clinical dose of 20 mg/day. In a 2-year carcinogenicity study in rats, an increased incidence of benign, ovarian granulosa-cell tumours was observed in female rats at dietary concentrations of 0.03% and 0.1% (equivalent to ~17 and 57 mg/kg/day). Systemic exposure (AUC) of bazedoxifene in these groups was 3 and 8 times higher than in patients. The observation of benign, ovarian granulosa-cell tumours in

female mice and rats administered bazedoxifene is a class effect of SERMs related to its pharmacology in rodents when treated during their reproductive lives, when their ovaries are functional and responsive to hormonal stimulation.

Renal tumours (adenomas and carcinomas) were observed with bazedoxifene in male rats at all dose levels tested (dietary concentrations  $\geq 0.003\%$ ; equivalent to  $\geq 1.3$  mg/kg/day), yielding systemic exposure (plasma AUC) 0.06 to 5 times that of patients at 20 mg/day. This occurred in conjunction with renal toxicity. Renal tumours were not observed with bazedoxifene in mice or female rats.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

The conjugated estrogens tablet core: Lactose monohydrate, microcrystalline cellulose, powdered cellulose, hypromellose, magnesium stearate, tribasic calcium phosphate, sucrose, hypolose, and macrogol 400.

Bazedoxifene active coating: Sucrose, hypromellose, sucrose palmitate, ascorbic acid, Opadry pink, Opaglos 2 Clear and Opacode black ink.

### **6.2 Incompatibilities**

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

### **6.3 Shelf life**

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

### **6.4 Special precautions for storage**

Store below 25°C.

Store in the original package in order to protect from moisture.

After opening the blister pouch, use within 60 days.

### **6.5 Nature and contents of container**

The tablets are provided in PVC/Aclar/PVC/Al blister packs of 7 or 28 tablets.

The tablets are packaged in a sealed blister card (Unit Fill: 1 tablet per blister cavity), which is then sealed along with an oxygen absorber in an aluminium foil laminate pouch.

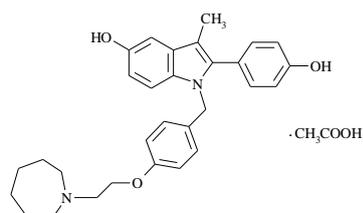
## 6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 Physicochemical properties

### Chemical structure

#### *Bazedoxifene*



The molecular weight is 530.65 and the molecular formula is  $C_{30}H_{34}N_2O_3 \cdot C_2H_4O_2$ .

Bazedoxifene is supplied as the acetate salt (bazedoxifene acetate) which has the chemical name 1H-Indol-5-ol,1-[[4-[2-(hexahydro-1H-azepin-1-yl) ethoxy]phenyl]methyl]-2-(4-hydroxyphenyl)-3-methyl-, monoacetate.

Bazedoxifene acetate is a white to tan powder. The aqueous solubility of bazedoxifene acetate is pH-dependent. Solubility is higher at lower pH. The solubility of bazedoxifene acetate in unbuffered sterile water was measured to be 923  $\mu\text{g/mL}$  at pH 5.4 (low solubility).

#### *Conjugated estrogens (CE)*

CE are obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine.

CE is a mixture of natural estrogens (of equine origin) composed principally of the sodium salts of water soluble sulphate esters of estrone, equilin and  $17\alpha$ -dihydroequilin together with smaller amounts of  $17\alpha$ -estradiol, equilenin, and  $17\alpha$ -dihydroequilenin,  $17\beta$ -dihydroequilin,  $17\beta$ -dihydroequilenin,  $17\beta$ -estradiol and  $\delta$ 8,9-dihydroestrone.

### CAS number

#### *Bazedoxifene acetate*

198481-33-3.

#### *Bazedoxifene*

198481-32-2.

## 7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

## 8. SPONSOR

Pfizer Australia Pty Ltd  
Level 17, 151 Clarence Street  
SYDNEY NSW 2000.

Toll Free Number: 1800 675 229.  
[www.pfizermedicalinformation.com.au/](http://www.pfizermedicalinformation.com.au/)

## 9. DATE OF FIRST APPROVAL

15 December 2016.

## 10. DATE OF REVISION

13 February 2024

® Registered trademark.

### Summary Table of Changes

Section changed	Summary of new information
6.5	Addition of statement regarding new packaging component (oxygen absorber).